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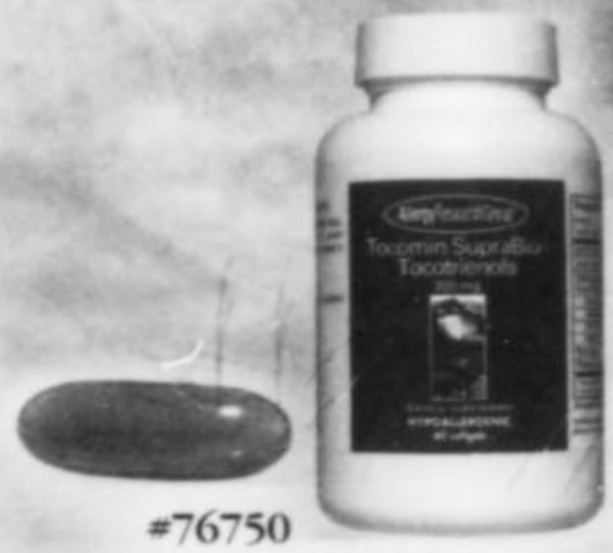

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Orthomolecular Medicine

Orthomolecular medicine is defined as the therapeutic use of substances that occur naturally in the body. Originally defined in the context of treating and preventing psychiatric diseases, the intent of orthomolecular therapy is to provide the optimal molecular environment for the brain and other tissues by altering the intake of nutrients such as vitamins (and their metabolites), minerals, trace elements, macronutrients, as well as other naturally occurring metabolically active substances.

Mission Statement

The mission of the Journal of Orthomolecular Medicine is to advance knowledge and improve the practice of orthomolecular medicine by educating practitioners of orthomolecular medicine, inspiring scholars, students and future leaders with novel, relevant and high quality metabolic research, clinical studies and reports, informative topic reviews and well-argued commentaries. The Journal aims to engage the orthomolecular medicine community by providing a forum for debate and the promulgation of new ideas.

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Rare Organic Causes of First Episode Psychosis

When evaluating patients having their first episode of psychosis, the work-up routinely involves a thorough search for medical and neurological conditions. This includes a complete medical evaluation, review of systems, physical examination with a neurological exam, and usually the following tests: a complete blood count, electrolytes, liver function, pregnancy (where appropriate), serum creatinine, blood urea nitrogen, thyroid function, sexually transmitted infections, and a toxicology screen.[1,2] Optional tests, such as erythrocyte sedimentation rate, antinuclear antibodies, and lumbar puncture might be necessary.[2] Should the neurological exam reveal any "asymmetry, weakness, or an altered sensorium" or if the psychosis is atypical (i.e., a first episode at age 70), brain imaging (computed tomography or magnetic resonance imaging) and an electroencephalogram should be obtained.[1] Additionally, the differential diagnosis should include the following possible diagnoses: schizophrenia and related disorders; mood disorders with psychosis; psychosis due to a medical condition; delirium due to a medical condition; dementia due to a medical condition; substance-induced psychotic disorder; substance-induced psychotic delirium; substance-induced intoxication or withdrawal; conversion disorder; and malingering.[2]

What if, after a thorough evaluation, the only possible diagnosis given was brief psychotic disorder since the duration of psychosis was less than one month? The patient would be promptly treated with atypical antipsychotics, benzodiazepines, and possibly other medications.[2] Eventually, after some period of time the patient would be discharged into the community with a follow-up plan to visit a psychiatrist. What would happen if this same patient became psychotic again, this time returning to the hospital four months from the initial episode with perhaps more pronounced memory problems and maybe some catatonia? This same patient would be more or less treated as before, but because this patient had returned with another psychotic episode, the diagnosis might be changed to reflect schizophreniform disorder because the patient's symptoms now have lasted for more than one month but less than six months. Let us once again imagine this same patient returning seven months since the first psychotic episode. Now the diagnosis has evolved into schizophrenia, and the patient would likely be given a new mix of psychiatric medications, possibly a different atypical antipsychotic, a benzodiazepine, a hypnotic agent for sleep, and an antidepressant for low moods.

The pattern I described is not that uncommon and many life events and problems can trigger patients into this never-ending cycle of psychosis, hospital readmission, and discharge. We very much want there to be obvious organic causes to the complexity of schizophrenia, and yet less than 6% of all first episode cases can be attributed to organic diseases.[3] Even for rare organic causes, such as gluten encephalopathy,[4] vitamin B_3 deficiency (i.e., pellagra),[5] and anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis,[6] the clinical reality is that they are hardly ever involved when psychosis rears its ugly head. It is interesting to note that some preliminary research has shown that 6.5% of 46 patients with first episode schizophrenia had NMDAR antibodies and fulfilled the diagnostic criteria for schizophrenia.[7] Thus, it is conceivable that as more is known about these rare causes of schizophrenia, more organic diseases might be uncovered with potentials for actual cure, which would be preferable to being maintained on psychiatric medications for life.

In this issue, I present an educational article on schizophrenia with its associated orthomolecular treatment. I specifically address management issues pertaining to cases where no underlying organic disease was found. I also discuss why so much uncertainty exists with the orthomolecular treatment of schizophrenia. I look forward to the day when organic causes can be found in more

than a small proportion of first episode cases. Until such time exists, the orthomolecular approach will continue to have limited efficacy in the treatment of schizophrenia because of the brain-disabling[8] and toxic effects[9] that psychiatric medications possess.

Jonathan E. Prousky, ND, MSc
Editor

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The Clinical use of Orthomolecules in the Treatment of Schizophrenia: Critical Reflections and Commentary

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Abstract *The syndrome of schizophrenia is marked by changes in the afflicted person's functioning, perception, thinking, and behaviour. The mainstay of treatment involves antipsychotic medications (either the older generation, and /or more commonly, the newer atypical antipsychotic medications), often combined with other psychiatric medications (e.g., anxiolytics, hypnotics, mood stabilizers, and/or antidepressants), as well as some psychoeducation. The "typical" schizophrenic patient seeking out the author's care has either been ill for a brief time (perhaps a year or less) or many years, has relapsed once or several times following the abrupt discontinuation of medication, has developed physical problems from medication (e.g., weight gain and tardive dyskinesia), and has accumulated a host of disabling behavioural and emotional coping strategies. Specific orthomolecular substances can reduce symptoms of psychosis, attenuate weight gain, and help to reduce symptoms of tardive dyskinesia and even neuroleptic-induced akathisia. Unfortunately, the long-term use of antipsychotic and other psychiatric drugs given to assuage symptoms of schizophrenia often cause devastating impacts on the bodies and brains of the individuals that take them. This makes it difficult, if not impossible for the orthomolecular approach to help patients fully recover.*

Introduction

The syndrome of schizophrenia is marked by changes in the afflicted person's functioning, perception, thinking, and behaviour. The onset can be sudden or take many years to reach some critical threshold, at which point the "illness" becomes so observable that it forces some type of action or intervention. Most individuals experience a prodromal phase in which there is gradual deterioration (e.g., social withdrawal, loss of interest in school or work, poor attention to personal hygiene, strange behaviour, and episodic outbursts of anger) eventually forcing families to recognize that something is wrong, although they might not be able to fully recognize how serious the situation is.[1] If afflicted individuals manifest overt symptoms of psychosis (i.e., some combination of delusions, hallucinations, disorganized speech and/or behaviours, and/or flattened affect or avolition), that normally results in a clinical diagnosis of schizophrenia particularly after other possible causes have been ruled-out.[1]

Schizophrenia has a prevalence of one percent. It characteristically affects males in their late teens or early twenties, and females in their late twenties or early thirties.[1] It is considered a polygenetic disorder. Environmental and developmental factors can influence an individual's vulnerability to being

diagnosed with schizophrenia.[2] Biomedical research has had a difficult time figuring out "how a genetically mediated, neurodevelopmental disorder is not expressed clinically until 1.5-3 decades postnatally, but then proceeds to progressively disable its victims."[2]

The mainstay of treatment involves antipsychotic medications (either the older generation, and/or more commonly, the newer atypical antipsychotic medications), often with combinations of other psychiatric medications (e.g., anxiolytics, hypnotics, mood stabilizers, and/or antidepressants), as well as some psychoeducation. While some afflicted individuals experience symptom reductions (and possibly remissions) when treated early in the course of their illness, the majority go on and off their psychiatric medications. This is believed to explain frequent relapses and remissions following treatment.[2] Unfortunately, this is associated with clinical deterioration and declining functionality over time.[2]

This difficult reality becomes a serious problem for clinicians trying to manage these individuals. Patients are often loaded-up on several psychiatric medications, which they have been told will be needed for the rest of their lives as a result of the expected chronicity of the syndrome. Many of these individuals detest how medications make them feel and frequently discontinue their pills abruptly with hopes of not needing them any longer. This typically results in destabilization and relapse, often requiring hospitalization and being re-prescribed several psychiatric medications. More plausibly, however, destabilizations can result from a) abruptly discontinuing or quickly tapering a biologically-habituated antipsychotic medication (as well as other medications), and/or b) neuroplastic changes arising from the frequent use of antipsychotic medication (i.e., drug-generated buildup of supersensitive dopamine receptors). Arguably those factors are more responsible for the chronicity of schizophrenia than medication non-compliance.[3,4]

Many sick individuals are pushed into assuming the role of the "mentally-ill" patient. They are often coerced into becoming lifetime consumers of powerful antipsychotic medications and other biomedical treatments. My clinical experience has shown that almost all such diagnosed individuals are held at bay and diminished by the very antipsychotic medications given as solutions to their psychotic symptoms. Antipsychotic medications work by suppressing or disabling the nervous system, which makes these individuals indifferent and apathetic.[5] These medications seem to undermine intrinsic motivational systems, reduce vitality, cloud and disable vulnerable brains, and make progressive and life-affirming changes extremely difficult to accomplish. I believe they also lead to behavioural disinhibition, and even a regression of emotional maturity.

I have seen too many individuals on these medications become self-absorbed, and focus on activities that involve immediate gratification (e.g., internet pornography, substance use/abuse, pathological gambling, and/or food-based addictions). They are rendered less capable of engaging in age-appropriate types of employment or volunteer activities. I don't believe that my observations are spurious since it is known that antipsychotic medications up-regulate the dopamine-type II receptors, which in turn reduces the functioning of dopamine-type I receptors. These changes have been linked to the presence of negative symptoms (i.e., defined as avolition, apathy, flat affect, and reduced social engagement).[6] Some highly questionable research demonstrates that schizophrenia is associated with hypofrontality,[6] which means reduced activation to the frontal regions of the cerebral cortex. I am more convinced that the observed hypofrontality results from taking medications that diminish motivation and cognitive capacity by undermining the brain's executive functioning.

Thus, the "typical" schizophrenic patient seeking out my care has either been ill for a brief time (perhaps a year or less) or many years, has relapsed once or several times following the abrupt discontinuation of medication, has developed physical problems from medication (e.g., weight gain and

tardive dyskinesia), and has accumulated a host of disabling behavioural and emotional coping strategies. Given this reality, how can I begin to mitigate symptoms and enhance patients' quality of life, while also helping to overcome the numerous negative effects that continue to accrue from the very psychiatric medications given to "stabilize" these individuals? This medical conundrum often overwhelms my clinical capabilities. Too few clinicians wish to honestly and openly address this obvious "elephant in the room."

I can offer hope, education and lifestyle counselling, and I can recommend evidence-informed orthomolecules* that may confer some symptom-reducing effect and/or perhaps lessen some of the negative impacts of antipsychotic medications. In this article, I will review some of best studied and easily obtainable orthomolecules for schizophrenia and comment on their clinical effectiveness. I will keep the discussions about biochemical mechanisms to a minimum since it is difficult to know precisely how particular orthomolecules work. Over decades, orthomolecular researchers and clinicians have noticed that certain orthomolecules have favourable effects. I will also attempt to show the different types of outcomes that can be expected when complementing psychiatric medications with orthomolecular substances.

Evidenced-Based Orthomolecules

While there are literally hundreds of studies on numerous orthomolecules for many health-related issues, only limited studies, some done decades ago, have evaluated the clinical merits of orthomolecules to address symptoms of schizophrenia. Without current robust research to support the clinical use of orthomolecules for schizophrenia, clinicians have to create reasonable plans for their schizophrenic patients based on clinical experience and not from numerous well-conducted clinical trials involving scores of patients.

*The term, Orthomolecule, refers to substances found naturally or normally in the human body, such as amino acids, essential fatty acids, hormones, minerals, and vitamins.

Glycine

One of more evidenced-based orthomolecules is glycine, an amino acid that functions as an inhibitory neurotransmitter in the central nervous system (CNS).[7] With respect to schizophrenia, the pathophysiology of the disorder is believed to involve hypofunction of glutamatergic N-methyl-D-aspartate receptors (NMDAR).[8,9] Glycine functions as a full agonist of the glycine site of the NMDAR, and has been shown to reduce negative symptoms of the disorder.[8] Based on my review of the pilot clinical trials done with this orthomolecule, the dose range is 0.8 g/kg per day.[10-14] It possibly benefits patients that are maintained on the older type or first-generation antipsychotic medication. Glycine might be contraindicated, however, when combined with the second-generation or atypical antipsychotic medication. One clinical trial showed a slight worsening of psychotic symptoms (as shown by an increase in the Brief Psychiatric Rating Scale scores) when glycine was combined with clozapine.[13] A similar clinical trial showed no added benefit (and no clinical worsening) when glycine was combined with clozapine.[14]

The use of glycine should be considered, even though it might only have potential value when prescribed to patients maintained on first-generation antipsychotic medication. In my opinion, antipsychotic medications are mostly responsible for the observed negative symptoms.[6] Glycine ought to be tried since it might reduce some of the medications' affect-suppressing and nervous system disabling properties. I have not observed any negative reactions from therapeutic doses of glycine, except that some patients do not like the taste even when mixed in diluted fruit juice. It needs to be taken away from meals and it requires good compliance.

N-Acetylcysteine (NAC)

NAC is a precursor to glutathione, which is presumed to be deficient in the brains of schizophrenic patients.[15] NAC has been shown to increase plasma glutathione levels.[16] NAC also supplies cysteine, serving as substrate for the glutamatergic

system; thus, NAC influences or modulates the glutamatergic system in a manner that might also reduce symptoms.[17] A clinical trial evaluated the safety and effectiveness of NAC (1,000 mg twice daily over 24 weeks) as augmentation to medicated patients with chronic schizophrenia.[18] Compared to placebo, the patients treated with NAC had improvements in their negative symptoms, global function, and akathisia. The improvements ceased within one month of discontinuing the orthomolecule. These improvements are noteworthy since all these patients were ill for an average of 12 years, and more than 60% were taking clozapine. A similar study showed statistically-significant improvements in negative symptoms among chronic schizophrenic patients given NAC (up to 2,000 mg per day) in combination with risperidone (taking up to 6 milligrams per day).[19] Thus, the benefits of NAC are similar to glycine, except that it can be safely combined with atypical antipsychotic medication and might also benefit akathisia. The only limiting factor is that some patients experience very unpleasant nausea or stomach upset, which can be intense so this orthomolecule should be taken away from food.

L-Lysine

By inhibiting L-arginine transport, the supplemental use of L-lysine is believed to decrease nitric oxide levels, which can favourably impact symptoms of schizophrenia (i.e., the "nitric oxide dysregulation hypothesis of schizophrenia").[20] In a single-blinded, randomized, crossover pilot study, L-lysine (6,000 mg daily) or placebo was given for four weeks to 10 patients with schizophrenia as an adjunct to their antipsychotic medication, and then treatment was crossed-over for another four weeks.[20] The use of L-lysine was associated with statistically-significant increases in L-lysine blood concentrations (eight out of 10 patients; $p<0.05$), and statistically-significant decreases in the positive symptoms of the disorder ($p<0.001$). The use of L-lysine did not perturb levels of the other amino acids tested, i.e., citrulline, arginine, proline, glutamate and alanine. However, based on further data analysis, the reductions in positive symptoms could not be solely attributed to that of the L-lysine supplementation. In addition, three patients self-reported improvements. Two patients noted decreases in their positive symptoms (i.e., auditory hallucinations) but those returned following trial termination. One patient reported improved attention while taking L-lysine, while another noted improved mental stability and memory capacity that continued for several weeks after the trial ended.

While these results are preliminary, they suggest that L-lysine augmentation might reduce positive symptoms of schizophrenia and perhaps confer some cognitive benefits as well. No significant adverse side effects were associated with L-lysine treatment, except transient gastrointestinal problems. The use of L-lysine was not associated with any extrapyramidal effects. The remarkable finding from this small pilot trial is that all the patients given L-lysine had been ill for a duration of 3-29 years, and were on various combinations of atypical antipsychotic medications (6 of 10 patients were taking at least two atypical antipsychotic medications).

It does appear that L-lysine can be combined with any type of atypical antipsychotic medication as a safe augmentation strategy, and could be given with the older types of antipsychotic medications as well.

L-Theanine

This amino acid apparently increases both dopamine and serotonin, although a study in rats showed that it might decrease serotonin.[21] It also increases alpha brain-wave activity, which facilitates relaxation without causing sedation.[21] In a randomized, double-blind, placebo-controlled trial, L-theanine or placebo was given to schizophrenic and schizoaffective disorder patients as an augmentation to antipsychotic medication.[22] Sixty patients were randomized to placebo or L-theanine (400 mg daily) for eight weeks, but only 40 patients completed the trial. Compared to placebo, L-theanine was associated with statistically significant reductions

in the following: anxiety (p=0.015), positive symptoms (p=0.009), and general psychopathology scores (p<0.001). According to the 5-dimension model of psychopathology, the use of L-theanine was also associated with statistically significant reductions over placebo in positive symptoms per the Positive and Negative Syndrome Scale (p=0.004), and activation factor (p=0.006).

Another study evaluated serum levels of various neurochemicals from the same 40 patients that completed the previous trial.[23] Analysis of the serum levels showed the beneficial effects of L-theanine to be associated with circulating levels of brain-derived neurotrophic factor and the cortisol-to-dehydroepiandrosterone ratio.

I have not observed any negative effects from the use of L-theanine and believe it would be safe to combine it with all classes of antipsychotic medication.

B-Complex Vitamins

Problems in one-carbon metabolism have been associated with schizophrenia, even though it is difficult to determine why this occurs.[24] Not all studies have shown patients with schizophrenia to have high plasma homocysteine levels or even methylene tetrahydrofolate reductase (MTHFR) polymorphisms. Those sorts of findings could explain problems with one-carbon metabolism. It is interesting to note that high plasma homocysteine levels have been associated with neurotoxicity through its effect on NMDARs. As discussed earlier, one biochemical theory of schizophrenia implicates NMDAR hypofunction as being etiologic.

In a randomized controlled trial, 42 schizophrenic patients with plasma homocysteine levels greater than 15 μmol/L were randomized to daily vitamin treatment (2 mg of folic acid, 25 mg of vitamin B_6, and 400 mcg of vitamin B_{12}) or placebo.[25] The vitamin and placebo groups were treated for three months, and then the groups were crossed-over for another three months (i.e., the group that had initially received vitamin treatment was put on placebo, and the group initially on placebo received vitamin treatment). Compared to placebo, the results revealed significant declines in homocysteine levels and statistically significant improvements in the positive and negative symptoms of schizophrenia (as measured by the Positive and Negative Syndrome Scale). In addition, neuropsychological test results were also improved (especially, the Wisconsin Card Sort Test, a measure of executive function) in the vitamin group compared to placebo. The authors were not sure why high homocysteine levels occur among some schizophrenic patients, but they did relate the high levels to low folate or vitamin B_{12} deficiency, polymorphism of MTHFR, obesity, smoking, or excessive caffeine consumption. The authors concluded that a subgroup of schizophrenic patients with high plasma homocysteine levels might benefit from the use of these B-vitamins, but they also noted that a high level of homocysteine might not be a perquisite to benefiting from the vitamin treatment.

These results are promising since therapeutic effects were noted from very low daily doses of orthomolecules. Additionally, these small amounts were able to confer benefits upon the executive functioning, which is usually impaired among patients with schizophrenia. I recommend that a good B-complex 50 or 100 is taken at least once daily and with additional folic acid so that the daily amount is at least 2 mg. B-complex vitamins will not interfere with any of the classes of antipsychotic medication, and are generally well tolerated as long as the vitamins are ingested with food. If taken on an empty stomach, the nausea and stomach discomfort can be substantial. B-complex vitamins will also cause yellowing of the urine, which is not a concern but patients need to be told about this so they don't become unduly worried.

Omega-3 Essential Fatty Acids

The therapeutic use of omega-3 essential fatty acids would probably help some of the cardiometabolic problems that are associated with antipsychotic medications, particularly the atypical ones. However, when looking at

the therapeutic value of omega-3 essential fatty acids, the research is not abundantly unanimous or even clear on the expected benefits with respect to symptom moderation. In the National Institute for Care and Health Excellence (NICE), the evidence is inconclusive, with four randomized controlled trials showing no benefit and another four randomized controlled trials showing benefit.[26] In the trials that showed benefit, patients with schizophrenia did have statistically significant reductions in positive and negative symptoms, but these improvements were likely minimal from a clinical perspective. In addition, the numbers of patients were low. Low patient numbers in a pilot trial can over-estimate the clinical benefits (i.e., a Type I error).

I continue to prescribe omega-3 essential fatty acids, but recognize that their clinical impacts are not large. Patients can experience mild gastrointestinal symptoms, such as diarrhoea, dyspepsia, or nausea.[26] The dose of eicosapentaenoic acid should be at least 2 g daily. It can be safely combined with all classes of antipsychotic medications.

Vitamin C (Ascorbic Acid)

The argument has been put forth that all humans suffer from an inherited condition known as hypoascorbemia, which means that a steady supply of vitamin C is needed from the environment (i.e., from food and/or supplements) to overcome our biochemical and physiological dependency on this vitamin.[27] In a study evaluating chronic schizophrenic patients, the plasma and urinary vitamin C levels of 35 schizophrenic patients were compared to an equal number of controls.[28] All subjects were given the same hospital diet and 70 mg of vitamin C daily for four weeks. Baseline plasma vitamin C values were lower in the schizophrenic patients ($p<0.05$), but normalized to approximately the same as the control group after the four weeks of treatment. The mean vitamin C levels as measured in a six hour urine collection were different among the low excretors of both groups, and this reached statistical significance ($p<0.05$) – 15.9 mg for schizophrenics and 39.5 mg for the controls.

When all the schizophrenic and control subjects were given a loading test of 1 g of vitamin C after the four weeks of 70 mg of vitamin C daily, the schizophrenic patients continued to excrete lower amounts of vitamin C in their urine compared to the control values. After the loading test, the plasma levels of vitamin C were different with the schizophrenic patients having a lower mean value than the controls ($p<0.05$). After one month of supplementation with 1 g of vitamin C, the plasma levels of each group equalized, as did the six hour urinary excretion rates. The authors of this study were in agreement with the hypothesis that "schizophrenic patients require higher levels of vitamin C than the suggested optimal ascorbic acid requirement for healthy humans."

A report by Smythies described some of the therapeutic functions that vitamin C has upon the brain including its ability to protect NMDARs from glutamate toxicity, antagonize the effects of amphetamines, enhance the therapeutic efficacy of the older class of antipsychotic medication (e.g., haloperidol), and prevent the auto-oxidation of dopamine to its toxic derivatives.[29] It is therefore biologically and clinically plausible that patients with schizophrenia require doses of vitamin C to optimize their metabolic needs. A randomized controlled trial combined 500 mg daily of vitamin C to atypical antipsychotic treatment for 8 weeks.[30] The results demonstrated that that addition of vitamin C improved antioxidant status and resulted in statistically significant reductions in symptoms as per decreases in the Brief Psychiatric Rating Scale.

Vitamin C can be safely combined with all of the usual treatments for schizophrenia. Since vitamin C has a short half-life, Hoffer suggested divided daily doses of up to 3,000 mg,[27] but starting doses can be between 500-1,000 mg. On the higher daily doses, some patients might experience gas, bloating, loose stools, and/or diarrhea until the dose is lessened.

Vitamin B_3

Hoffer and other researchers discovered a relationship between vitamin B_3 (i.e., niacin/nicotinic acid or niacinamide/nicotinamide), pellagra and schizophrenia. It is known that a subset of patients with schizophrenia will have a reduced skin flush response to topical methylnicotinate,[31,32] and reduced skin sensitivity has been associated with greater functional impairment among patients with schizophrenia.[33] Research by Miller et al has shown an in vivo impairment in the ability to synthesize dietary tryptophan to nicotinamide adenine dinucleotide because of an up-regulation of the kynurenine pathway in some deceased patients with schizophrenia.[34] The authors reported that these results might be due to a diminished niacin effect; possibly, the result of depressed production or reduced signal transduction via the niacin receptor. They noted that niacin or its congeners are obligatory regulators of this biochemical pathway and should be capable of restoring homeostasis. In follow-up research by Miller and Dulay, evaluations of post-mortem brain tissues of schizophrenic patients showed that the protein for the high-affinity niacin receptor was down-regulated in the anterior cingulate cortex.[35] This suggests that the peripheral defects reported above also extend to the brain.

It should be noted that the number of post-mortem brains evaluated was very small, which makes it very difficult to generalize these unique findings to a broader group of patients with schizophrenia. While this research excluded smoking and antipsychotic medication as possible causes,[30,31] it is unclear whether these findings reflect some unique biochemical abnormality specific to patients with schizophrenia. It seems more plausible that lifestyle, the impacts of substance use and/or abuse, the neuroplastic changes resulting from antipsychotic and other psychiatric medications, as well as other unknown (but explainable) factors are more responsible for these findings. Even so, these findings suggest an increased need for vitamin B_3 among patients with schizophrenia.

I continue to use vitamin B_3 even though modern randomized studies are summarily lacking. When Hoffer reported his excellent outcomes from several randomized controlled trials decades ago, vitamin B_3 was given to patients very early in the course of their psychoses along with usual care (i.e., some combination of psychiatric medications and sometimes electroconvulsive therapy) and compared to usual care by itself.[36,37] It is a challenge to apply these clinical trial results to the mental health care of today's patients since the current psychiatric care provided to patients with schizophrenia is vastly different from the 1950s and 1960s. Even Hoffer reported that vitamin B_3 cannot overcome the "tranquilizer psychosis," a term he used to describe the harmful and often devastating effects that atypical antipsychotic medications have upon the bodies and brains of individuals taking such medications.[38] Hoffer observed clinically that no amount of vitamin B_3 could reverse the tranquilizer psychosis that patients experienced from atypical antipsychotic medications, and thus patients were not likely to recover unless they were tapered down or weaned off of psychiatric medications (after stabilizing).

Hoffer also reported on the efficacy of vitamin B_3 when administered to patients with chronic schizophrenia. Chronic patients required vitamin B_3 treatment for five or more years in order to derive observable benefits.[39,40] In one study involving 32 chronic patients, all the patients failed to respond to vitamin B_3 after two years of use. Nineteen of the patients discontinued the vitamin, and the remaining 13 patients continued with the vitamin treatment. Data was obtained for the years, 1956-1957, 1958-1959, 1960-1961, 1962-1963, and 1964.[39] Of the patients not on niacin, the mean number of days spent in hospital were 691 compared to 79 in the niacin group. Also, the proportion of time spent in the hospital was substantially less for the chronic patients who remained on the vitamin. In another analysis of 27 chronic patients who had been under treatment for at least 10 years, consistent treatment with vitamin B_3 produced the following results: 11 patients were able to work; two patients were able to marry and

look after their family and home; two patients were single mothers able to take care of their children; and three patients were able to manage their own businesses.[40] These results are striking when one considers the state of these patients prior to receiving orthomolecular care. The average age of these patients was 40, the majority of them were ill for seven years before they sought treatment from Hoffer, and all had been unresponsive to previous treatments. It should be noted, however, that when Hoffer treated these chronic patients with success they were not on atypical antipsychotic medication, which as mentioned above, undermines any potential efficacy that niacin possesses. Unfortunately, there have been no recent randomized controlled trials evaluating the efficacy of vitamin B_3 for early schizophrenia or first-episode psychosis, or for patients with chronic schizophrenia.

I am not sure if Hoffer's recommended dose ranges can help, given the current reality of patients loaded-up on psychiatric medications. It is doubtful that vitamin B_3 in any amount will overcome the negative psychoactive effects that these medications induce. I have not observed too many successes with optimal doses of the vitamin (3,000 mg or more daily) among chronic patients also taking prescribed cocktails of psychiatric medication that typically include at least one or more of the atypical antipsychotics. In my opinion, the capacity of vitamin B_3 to mitigate symptoms of psychosis has diminished significantly as a result of how patients with schizophrenia are managed by today's physicians.

What can reasonably be expected from vitamin B_3 treatment? My clinical experience has shown some ability of vitamin B_3 to help with the worrisome cardiometabolic effects of antipsychotic drugs, improve cognitive function, and somewhat lessen the intensity of psychotic symptoms, but these therapeutic effects are usually temporary. Normally something happens to necessitate a change in antipsychotic medication, which tends to result in further complications and less therapeutic responsiveness from vitamin B_3 or any other orthomolecular treatment.

Orthomolecules for Tardive Dyskinesia, Akathisia, and Weight Gain

Tardive dyskinesia (TD) is a devastating involuntary movement disorder that can result from treatment with antipsychotic medication. Sadly, this may not be reversible even when medication is discontinued. TD affects the orofacial area, but all parts of the body can be affected manifesting as myoclonic jerks, tics, chorea, and dystonia. These symptoms increase when patients are stressed or aroused, lessen when patients are relaxed, and remit during sleep.[41] TD is associated with an increase in mortality ($p<0.001$), but this statistic can become nonsignificant if one factors in age and the type of antipsychotic used.[42] Patients on older (i.e., first generation) antipsychotics were twice as likely to die compared to those on atypical antipsychotics ($p<0.02$), and for patients between 53 and 65 years of age, the use of older antipsychotics was linked to a sevenfold increase in mortality.[42]

Several orthomolecular treatment options have been studied and found capable of reducing symptoms of TD. Vitamin E (D-alpha tocopherol) has been shown to reduce symptoms of TD[43] likely through its antioxidant effects and by increasing superoxide dismutase levels.[44] Not all studies with vitamin E have shown benefit.[45] In a randomized clinical trial, the use of 10 mg of controlled-release melatonin was found helpful in reducing symptoms of TD over a duration of six weeks.[46] In another trial, 20 mg of immediate-release melatonin was significantly helpful in treating TD among only two patients given the hormone. The remaining patients did not benefit from it.[47] Since two patients from this study had a marked benefit from melatonin, it might benefit a subgroup of patients who have this negative outcome from antipsychotic medication. Melatonin helps by attenuating the dopaminergic activity in the striatum and the release of dopamine from the hypothalamus; which suggests why it might help in the treatment and prevention of TD. Vitamin B_6 can also reduce symptoms of TD[48,49] and even acute neuroleptic-induced akathisia.[50,51] The mechanism of action for vitamin B_6's effect upon TD and

akathisia is unclear, but it may influence the dopaminergic system and counteract some of the negative effects that the medications have upon the motor system.

Clinicians should choose 1-2 options among all the orthomolecular treatments identified here and assess the benefit over a period of 2-3 months. If no beneficial results are observed, discontinue the orthomolecular treatment(s) and try 1-2 others for another 2-3 months. If no change in TD and/or akathisia results after several therapeutic trials, it would be prudent to refer the patient to a neurologist who focuses on movement related disorders due to antipsychotic medication. The suggested dosages for therapeutic trials include: Vitamin E (800 IU twice daily), vitamin B_6 (600 mg twice daily for only 5 days for acute neuroleptic-induced akathisia, and then 400 mg daily thereafter for TD), or melatonin (10-20 mg of a controlled-release preparation at bedtime).

With respect to weight gain, which can be tremendous from the atypical antipsychotic medications, only alpha-lipoic acid has shown the ability to attenuate some of the abnormal increases in body weight.[52,53] Alpha-lipoic acid should be used in daily doses of 1,200 mg since this dose can arrest some of the significant weight gain associated with these medications.[53] I have not seen any patient experience negative effects from the daily use of alpha-lipoic acid.

Summary

When reviewing the potential therapeutic benefits from the above-mentioned orthomolecules, it appears that they can moderate psychotic symptoms and improve cognitive function. In **Table 1** (p.150) is a summary of this data.

Table 2 (p.150) lists the orthomolecules with some potential in reducing some of the devastating neurological and cardiometabolic effects from antipsychotic medication.

Discussion

When thinking critically about the effectiveness of the orthomolecular approach, as applied to patients with schizophrenia, the outcomes are not going to be too substantive as long as patients are maintained on high doses of antipsychotic medication and other psychiatric medications. As noted earlier, patients become tranquilized as a result of their psychiatric medications, especially the atypical antipsychotic ones, which create enormous dependency states associated with numerous brain- and body-based harms and complications.[54] These effects undermine the benefits of orthomolecular substances, and cause massively repressive effects upon human potential and growth.[55]

How are clinicians supposed to work within this paradigm of mental health care that aggressively promotes the long-term use of psychiatric medication? There are no straightforward solutions, and as stated earlier, I am often overwhelmed trying to assist patients ill with schizophrenia who appear to have been damaged by the very psychiatric medications intended to help them.

In my experience, as long as patients chronically remain on their potent mix of psychiatric medications, their outcomes are not good. Schizophrenia is not a degenerative brain disease, and some 20-54% of patients can fully recover.[56] The long-term use of antipsychotics leads to fewer recoveries[56] compared to being off these medications for many years.[57,58] These results have little to do with personality factors or the premorbid mental states of patients, and much more to do with the very psychiatric medications promoted as "essential" components to their full recovery. As is known, "these patients are typically forced to take heavy tranquilizing drugs or even undergo electroconvulsive shock therapy, severely impairing their most important resources-hope, meaning, and connection with their aliveness."[56] Full recoveries while taking orthomolecular substances or even benefiting from well-intentioned psychosocial interventions are unlikely to happen when patients are loaded-up on their cocktails of psychiatric medications.

Since the majority of highly industrialized countries provide antipsychotic and other psychiatric medications for most patients presenting with psychosis, it is unlikely that

Table 1. Symptom-Moderating Effects of Specific Orthomolecular Substances

Potentially improves positive symptoms	Potentially improves negative symptoms	Potentially improves cognitive function
- L-lysine - L-Theanine - B-Complex vitamins (especially, vitamins B_6, B_{12}, and folic acid) - Omega-3 essential fatty acids - Vitamin C - Vitamin B_3	- Glycine (best to combine only with first-generation or the older antipsychotic medications) - NAC - B-Complex vitamins (especially, vitamins B_6, B_{12}, and folic acid) - Omega-3 essential fatty acids - Vitamin C - Vitamin B_3	- L-lysine - Vitamin B_3

Table 2. Mitigating the Adverse Cardiometabolic and Neurological Effects with Orthomolecular Substances

Potentially improves cardiometabolic effects	Potentially improves TD symptoms	Potentially improves Acute Neuroleptic-Induced Akathisia
- Omega-3 essential fatty acids - Vitamin B_3 (must be niacin/nicotinic acid) - Alpha-lipoic acid (to attenuate weight gain associated with atypical antipsychotic medication)	- Vitamin E (D-alpha tocopherol) - Melatonin - Vitamin B_6	- Vitamin B_6 (high daily doses are only to be used for 5 days)

the antipsychotic treatment imposed during acute psychotic crises is going to change anytime soon. There is a dearth of residential alternatives to hospitalization where patients could receive alternative support in an environment that focuses on meaning, choice, hope, autonomy, and other relevant existential elements, and where the use of antipsychotic medication is minimized or not prescribed at all. Because there currently are no thriving alternatives to hospitalization, what somehow needs to happen is a shift away from enforcing psychiatric medications for life, and a focus on providing short-term psychiatric medication (if determined to be necessary) only to assuage acute psychotic crises. This could then be followed by life-affirming treatments, such as restorative or-

thomolecular regimens and supportive use of psychological therapies, psychoeducation, proper housing, adequate food and access to social services that focus on self-management and personal empowerment strategies.

Conclusion

The mortality for schizophrenics is 15-20 years earlier than the general population.[59] I contend that the long-term reliance on high doses of antipsychotic and other psychiatric medications given to these individuals result in poorer long-term prognoses and contributes to early mortality. These pills make it very challenging for the aforementioned orthomolecules to lessen psychosis and other psychiatric symptoms, and ameliorate drug-induced neurological damage (if present).

However, as this article points out and as Abram Hoffer reported over his decades-long career, it is possible for orthomolecular regimens to help some patients, particularly those with early-onset schizophrenia. In acute cases, high doses of antipsychotic medications may only be needed for brief periods until patients stabilize at which point they can continue on low-doses of antipsychotic medications while also taking orthomolecular regimens which can gradually help patients recover normal or have near-normal function.

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Competing Interests

The author declares that he has no competing interests.

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High Dose Intraveneous Vitamin C and Chikungunya Fever: A Case Report

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Abstract *The Chikungunya (CHIKV) fever is a viral disease produced by a single-stranded RNA Alphavirus from the Togaviridae genus. Its transmission occurs only through mosquito vectors, principally Aedes aegypti. It requires a human-mosquito-human transmission cycle. It is associated with severe arthritis/arthralgias, myalgias, high fever, headache, and maculopapular rash. Joint ache appears to be symmetrical. The virus has an incubation period of 2 to 7 days, where the high fever is typically presented. It is followed by arthralgias and myalgias, and rashes, which last for 3 to 5 days. However, the arthralgias can persist for months after the infection, which can contribute to severe arthritis. As of now, no vaccine exists for the virus and no official treatment has been developed aside from standard procedures of the use of acetaminophen (paracetamol), and non-steroidal anti-inflammatory drugs. This is a case report of a 54-year old Hispanic individual that reported left shoulder pain, left knee pain and fever. The symptoms started on a Saturday in September 2014 in middle of the night. The patient was treated with high doses of intravenous vitamin C over two days. The symptoms resolved after the infusions without any side effects. Based on the positive outcome in this case, we propose that intravenous vitamin C should be studied further as a potential treatment for acute viral infections.*

Introduction

The Chikungunya virus (CHIKV) is a single-stranded RNA Alphavirus from the Togaviridae genus.[1] It was first isolated in humans in 1952 in Tanzania. Its transmission occurs only through mosquito vectors, principally *Aedes aegypti*. It requires a human-mosquito-human transmission cycle. Over the years, it has been ignored as a potential threat, mostly affecting developing countries. At this moment, no vaccine exists for the virus and no official treatment has been developed aside from the standard procedures of the use of paracetamol or acetaminophen, and non-steroidal anti-inflammatory drugs for symptom control.[2] Infection with chikungunya virus is rarely fatal, but the joint pain can often be severe and debilitating. The acute phase of the infection usually last 5 to 7 days. A temporary slight improvement is often followed by pain of moderate to severe intensity that can lead to temporary disability.

The virus mainly affects the human endothelial and epithelial cells known as fibroblasts. These fibroblasts usually make up the muscle and joint tissue. As the infection progresses, these fibroblasts are damaged and epithelial and endothelial cells die. The

injury to the fibroblasts results in muscle and joint pain.

For many years, it has been widely known that ascorbic acid (vitamin C) has a variety of functions with clinical efficacy. It is a water-soluble antioxidant, and has been used to prevent many diseases or infections like the common cold and other viral infections.[3-6] Ascorbic acid scavenges reactive oxygen species (ROS), increases vascular and connective tissue integrity, improves immune function, and assists in leukocyte phagocytic functions.[7]

Vitamin C supplemented orally has its limitations in achieving high blood (i.e., plasma) levels, whereas the use of intravenous vitamin C (IVC) can reach blood levels that possess distinct clinical and pharmacological advantages. Vitamin C is absorbed in the gastrointestinal tract, where the body metabolizes a limited amount and the rest is excreted through the kidneys.[8] However, if the vitamin is administered intravenously it can reach plasma concentrations that are 30 to 70 times higher than the oral pathway.

Ascorbic acid is also a nutrient for the immune system. Treatment of ascorbic acid in vitro resulted in an increase in T-cells and natural killer (NK)-cells, which constitute one of the main components of the adaptive immune system which fights against viruses and intracellular bacteria.[3] It has been suggested the same effect can be achieved by IVC administration.

Here we report a case of Chikungunya fever, treated with high doses (100g/day) of IVC in a period of two days and without any side effects.

Case Report Presentation

This is a case of a 54-year old Hispanic individual who reported severe arthralgia, left shoulder pain, left knee pain as well as a maculopapular rash and a high fever. The symptoms started on a Saturday in September 2014 a few hours before dawn. Next day the patient had a lab test for Chikungunya and dengue. He eventually was found to be positive for Chikungunya via an elevated immunoglobulin M (i.e., IgM) titre. The patient was treated with high doses of IVC (100g/day) for a duration of two days. In relation to lab parameters before treatment, the only abnormality was an extremely large increase in C-reactive protein/CRP (26.9 mg/L). This CRP measure after treatment was reduced to 15.8 mg/L. The symptoms of pain, fever, and rash resolved after the infusions without any side effects. The symptoms improved substantially in 24 hours and were absent the next day.

Discussion

Growing evidence has suggested a close correlation between oxidative stress and viral infectious disease.[9] The elevated oxidants induced by viral infection include nitric oxide radicals, superoxide anions, hydroxyl radicals and their by-products (such as hydrogen peroxide), which may all contribute to viral pathogenesis, the modulation of cellular responses, and the regulation of viral replication and the host defense.[9] Many of these oxidants may be harmful to the host cells if they are released into the extracellular medium.[10,11]

Vitamin C is an efficient antioxidant, and possesses anti-viral activity. For example, it has been shown that vitamin C is an essential factor in the production of the anti-viral immune response during the early phase of viral infection through the production of type I interferons, which up-regulates NK cell and cytotoxic T-lymphocyte activity.[12] Also, studies have indicated that ascorbic acid can be used as an inactivating agent for both RNA and DNA viruses, affecting viral infectivity.[5] In addition, ascorbic acid can detoxify viral products that produce pain and inflammation.[6] All this evidence confirms the effectiveness of ascorbic acid against viral infections, and Chikungunya fever, as suggested by the patient's swift response to IVC. Furthermore, no side effects resulted during or after the treatment. Based on the positive outcome in this case, we propose that IVC should be studied further as a potential treatment for acute viral infections.

Competing Interests

The authors declare that they have no competing interests.

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The Role of Mitochondria in Cancer and Other Chronic Diseases

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Abstract *Nutrition is the foundation and basis of good health; therefore, it stands to reason that a proper diet would assist in the prevention of common 21st century chronic diseases such as heart disease, diabetes, neurodegenerative diseases, and cancer. In this article we explain the roles of mitochondria in health, and the biochemistry of mitochondria in degenerative disease. We examine the role of oxygen in both (aerobic) oxidative phosphorylation (OxPhos) and (anaerobic) glycolysis, and how the latter may contribute to chronic disease states. We discuss the biochemical mechanisms behind adenosine triphosphate production and the simultaneous production of Reactive Oxygen Species (ROS) (free radicals), and the chronic effects of cellular ROS damage. Lastly, we discuss the cellular health-enhancing effects of reductive molecules (antioxidants) and an alkaline environment, and how this contrasts with an acidic environment/ diet, which contributes to chronic disease and the pathological state.*

Mitochondrial Basics

Mitochondria serve several important cellular roles, but first, we shall discuss some background history, structure and the roles mitochondria play in cellular health. It is generally recognized and agreed that mitochondria originated from an aerobic bacteria approximately 1-3 billion years ago, which merged with a pre-existing unicellular organism. Both organisms developed a symbiotic relationship which provided a way to create aerobic cellular respiration and produce much more energy. This in turn, supports the development of complex multi-cellular aerobic organisms. Mitochondria are the only subcellular organelle/organism with their own mtDNA.[1]

Because mtDNA is maternally transmitted by the ovum at conception (inherited from one's mother), its genetic defects or variants, deficiencies (if any) are limited to the mitochondria; the cellular-nuclear DNA (nDNA) is governed by Mendelian inheritance principles. In contrast to nDNA which is made up of 3.3 billion base pairs (bp) of genes, mtDNA is circular and composed of 16,569 bp. These bp include 37 genes, of which 24 encode for mitochondrial translation and 13 encode for the cellular respiratory chain.[2] nDNA is protected by histones which shield nDNA from free radical damage, however, mtDNA is not protected by histones, so they are more susceptible to oxidative damage.[3] mtDNA may generate up to 10 times the number of

nDNA mutations for two reasons – mtDNA resides close to the electronic transport system (ETS) inside the inner mitochondrial membrane and mtDNA lacks repair mechanisms, so once damaged, the mitochondria may be slated for apoptosis.[4]

Mitochondria Structure and Roles

The number of mitochondria per cell is energy/function dependent; i.e., those cells that require and expend the most energy contain the highest number of mitochondria. Most cells have between a few hundred to over 20,000 mitochondria; they are concentrated most heavily in cells of the heart, brain, liver, muscles, gastrointestinal tract, and kidneys.[5]

Mitochondria are composed of two membranes. The more porous outer membrane contains porin and allows molecules up to approximately 10 kDa to freely diffuse across the membrane. The inner, more tightly constructed (less permeable) membrane contains cardiolipin, a phospholipid which has both a higher affinity for inner membrane proteins, and, having two unsaturated bonds, is more susceptible to oxidative damage. Components of the electron transport system (ETS) are found along the inner membrane. The space between the two membranes is the intermembrane space where Cytochrome c is found. Inside the inner membrane is the mitochondrial matrix which contains many of the enzymes necessary for adenosine triphosphate (ATP) production (enzymes associated with the Kreb's Cycle), as well as the mitochondrial genome.[6]

Mitochondria play many important roles in human biology, including synthesis of heme, lipids, amino acids and nucleotides. As mentioned above, they are involved in initiating cellular apoptosis. Their most important role, however, is the production of ATP. Mitochondria generate 95% of the ATP in the cell, and rely on ATP for its own functions.[7,8]

Due to the location of the ETS adjacent to the inner mitochondrial membrane, the generation of free radicals as a normal part of oxidative phosphorylation (production of ATP), as well as the lack of histone protection for mtDNA, much oxidative damage can occur to mitochondria, and indeed does occur in normal physiological reactions as well as in chronic disease. Later, we will discuss the role that an alkaline diet can play in preventing much of this oxidative damage.

Review of ATP Biosynthesis

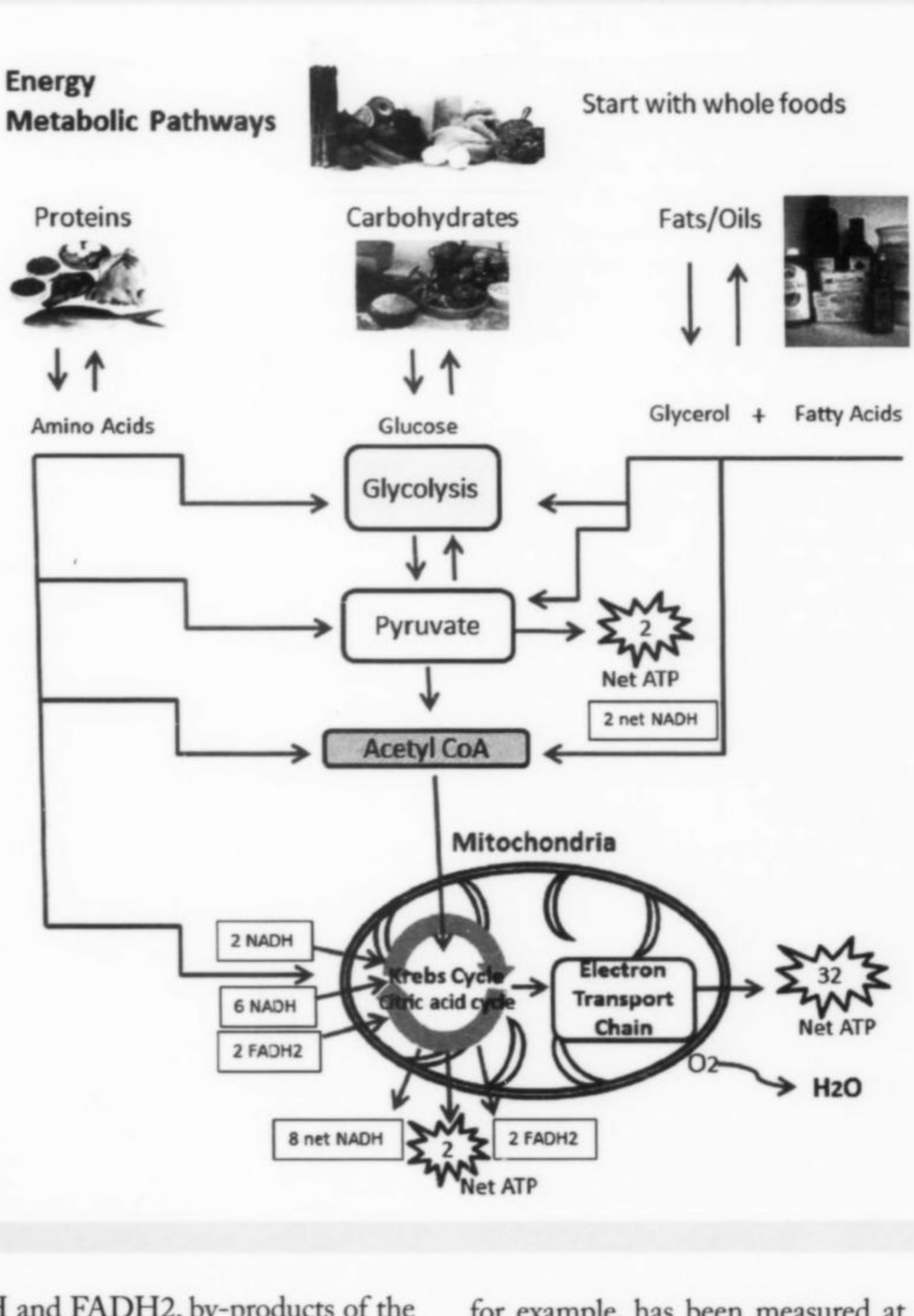
As stated above, the primary role of mitochondria is to synthesize ATP (cellular energy). This process is also known as cellular respiration. As humans, we derive all our energy from the food we eat, which the mitochondria metabolize into glucose, amino acids and fatty acids. Because we derive all our cellular energy from the food we eat, this fact emphasizes the point that eating whole food is necessary for proper ATP production and general cellular functions. Recent research has linked all chronic disease, including cancer, to deficiencies in mitochondrial structure and function.[1]

The Role of Oxygen in Both (Aerobic) Oxidative Phosphorylation and (Anaerobic) Glycolysis

As presented in **Figure 1,** (p.159) the "normal" process of oxidative phosphorylation (OxPhos) creates approximately 38 ATPs per glucose molecule and approximately 90% of the cell's energy requirements. Under normal aerobic conditions, pyruvate is oxidized by NAD+ and a dehydrogenase enzyme that converts pyruvate to Acetyl-CoA and CO2. This reaction requires oxygen to oxidize NADH back to NAD+ to continue the metabolic process.[9]

This section will provide a simplified explanation of the ETS and OxPhos in the inner membrane of the mitochondria. Research has identified five protein complexes on the inner mitochondrial membrane related to the ETS and OxPhos processes; Complexes I, II, III, IV are part of the ETC, and Complex V is where OxPhos or the conversion of ADP to ATP actually takes place. This process requires co-factors that actually carry the electrons "down" the ETS such as cytochrome C and Co-Q_2 as illustrated in **Figure 2.** (p.160) The entire process is actually one of oxidation

Figure 1. The oxidative phosphorylation process.



of NADH and FADH2, by-products of the Kreb's Cycle, to H_2O. [10]

Complexes I, III, and IV "pump" protons from the inner membrane across the membrane into the intermembrane space, creating a "proton gradient" that is necessary for ATPase conversion of ADP to ATP (phosphorylation). The potential of hepatocytes, for example, has been measured at 170mV, but the normal cell potential is 50-70 mV. A proton gradient is necessary for efficient ETS function. The combination of movement of protons "down" the ETS and the phosphorylation of ADP in Complex V is called the coupling of cellular respiration with the synthesis of ATP. It is said that the efficiency with

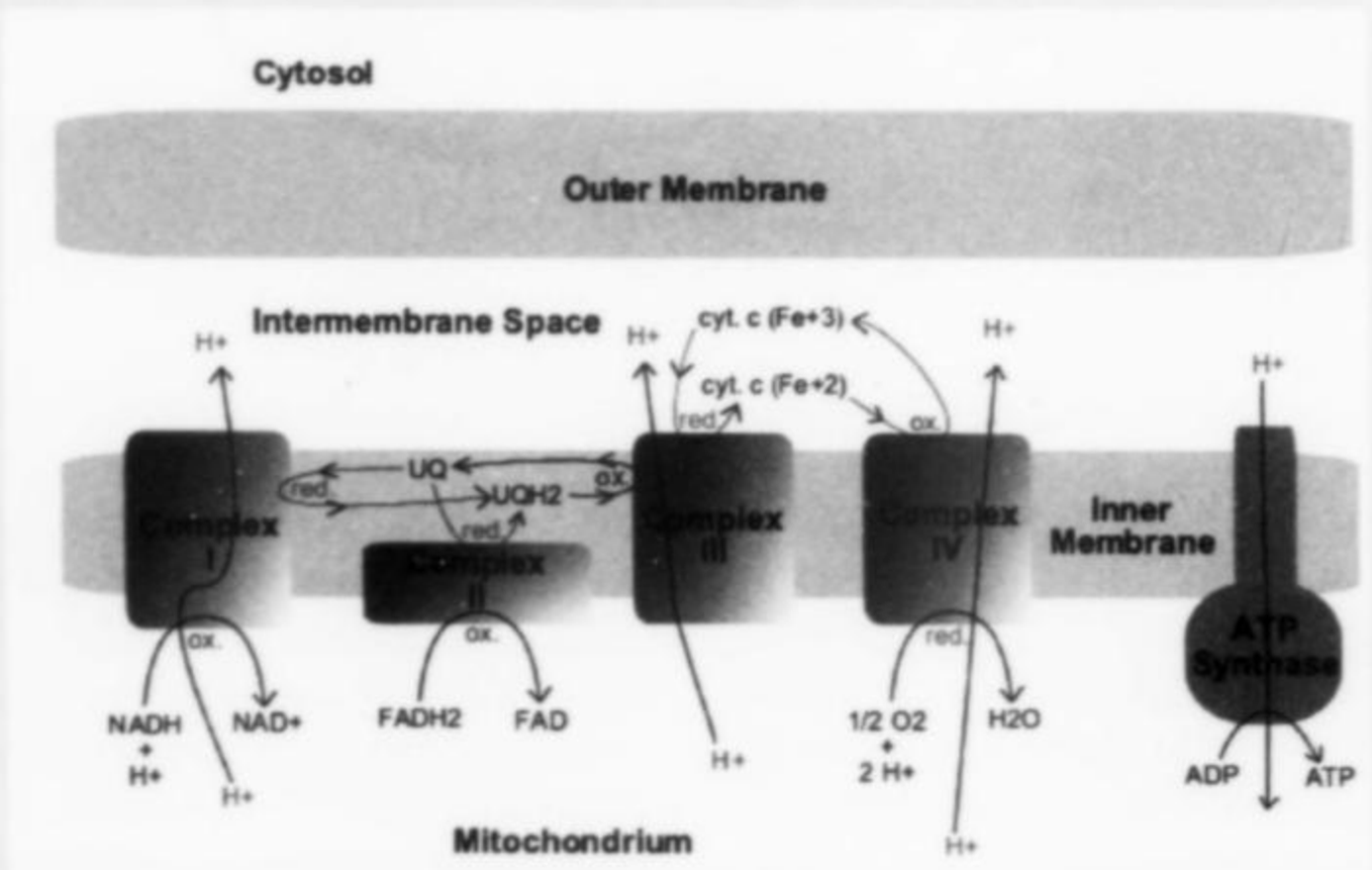
which foods are metabolized and converted to energy is determined by the efficiency of this "coupling" process. It is estimated that each complex pumps four protons across the membrane.[10,11] The "pumping" of protons into the intermembrane space helps maintain an alkaline pH inside the mitochondria, which then creates a negative potential with respect to the cytosol.[11] Acidic substances, xenobiotics, and drugs can also "uncouple" the ETS from OxPhos. As previously stated, the entire ETS and OxPhos process produces approximately 38 ATP.

Because ATP production occurs in the cristae of the inner membrane, close to the ETS where protons are "pumped" and occasionally "lost," the mitochondria are subject to great oxidative damage themselves by their own processes. Although aerobic OxPhos is the optimal process for producing ATP, it is not without inherent danger to the mitochondria themselves, as it also produces ROS such as the superoxide radical O_2.-, hydrogen peroxide H_2O_2, the hydroxyl radical HO. ,the perhydroxyl radical HO_2. , and peroxynitrite ONOO- . During normal OxPhos, 0.4 – 4% of all oxygen consumed is converted in mitochondria to superoxide O_2.-.[1] These ROS contribute to enzymatic damage, membrane damage and subsequent apoptosis. Not only do ROS accumulate with age, but they negatively affect mtDNA replication and repair processes. Organelles that have sustained damage to their DNA, membranes, or respiratory chain (ATP synthesis) proteins will suffer from a chronic energy shortage and diminished or nonexistent proton gradient.[12] Defective mitochondria accumulate most in ATP-active organs such as the brain, heart and muscle, which may partly explain the increasing incidence of chronic diseases involving these organs. These ROS can be "paired" and neutralized in the cell with a diet high in antioxidants, found in a typical alkaline diet rich of fresh fruits and vegetables.

Anaerobic Glycolysis

This discussion about ROS damage to mitochondria relates to anaerobic glycolysis. From the point in the metabolic pathway where pyruvate metabolizes to Acetyl-CoA, pyruvate can also take another form as lactate ($C_3H_5O_3$-) under conditions of low oxygen. The attention should be directed to the one-way arrow emerging from pyruvate ($C_3H_4O_3$) to Acetyl-CoA ($C_{21}H_{36}N_7O_{16}P_3S$) to indicate that, at this point in the metabolic process, pyruvate can only metabolize to

Figure 2. Oxidation of NADH and $FADH_2$·



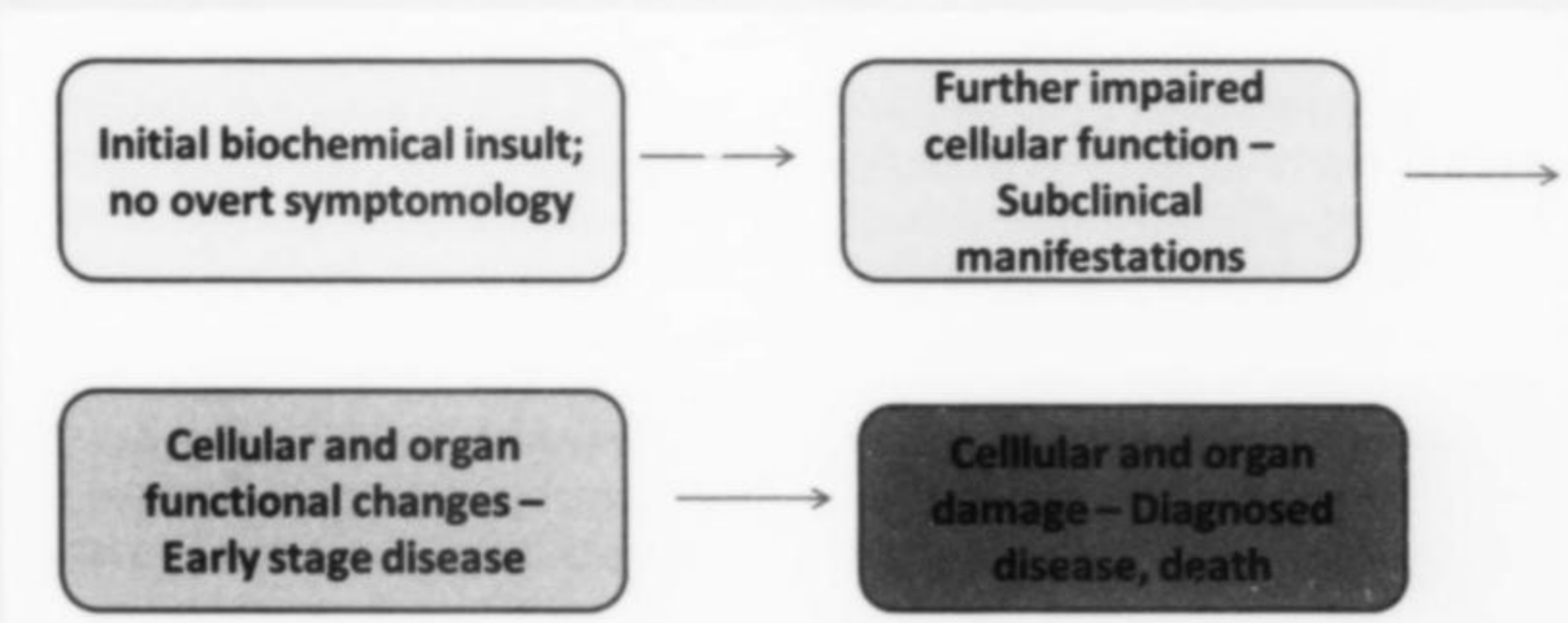
Acetyl-CoA in the presence of oxygen. When muscles have over-exercised and "used up" the available oxygen, pyruvate cannot convert to Acetyl-CoA and instead turns to lactic acid ($C_3H_6O_3$). This phenomenon occurs during heavy exercise or stress, for example, but can also occur in the initial stages of cancer and other degenerative and chronic diseases which affect cellular integrity. Lactic acid creates an acidic cellular environment that, if not immediately corrected, contributes to a chronic acidic cellular environment which is conducive to cellular breakdown, loss of function and predisposition to cancer. The usual disease progression may follow the pattern depicted in Figure 3. (below)[13]

Recall that mtDNA lacks protective histones and repair mechanisms; therefore, they are more susceptible to oxidative damage. And although each cell contains numerous mitochondria (from hundreds to over 20,000), one would think that occasional mitochondrial damage would not significantly impact a cell or an organ. And occasional mitochondrial damage does not affect cellular or organ function. However, years of cumulative oxidative damage to both mtDNA and subsequently nDNA does indeed adversely affect cellular and organ function which leads to disease states, cancer and aging.

ROS Damage

As stated above, a two-edged sword regarding ATP production is the simultaneous production of necessary ROS that may have a role in gene regulation and excessive damaging ROS leading to the disease state, under both aerobic and anaerobic conditions. One explanation for how ROS damage contributes to chronic disease conditions is that excess calories (or poor quality calories), and the lack or excess of exercise generate more electrons than the ETS can handle, leaving more electrons in the inner membrane space (because they can't be pumped back out into the intermembrane space). This adversely affects the proton gradient necessary for ADP coupling with P to create ATP, stalling the ETS process. Additionally, with less oxygen available to pair with the protons created in the ETS process, the cells cannot make H_2O as a by-product of OxPhos, so more ROS accumulate in the cells, contributing further to mtDNA damage and subsequent nDNA damage.[14] ROS contributes to mtDNA damage/deletions/mutations, and as less ATP is produced and cellular functions diminish, subsequent replicated mitochondria become less and less robust and unable to successfully carry out cellular and organ functions, thus contributing to chronic degenerative disease.

Figure 3. Anaerobic glycolysis and disease progression.



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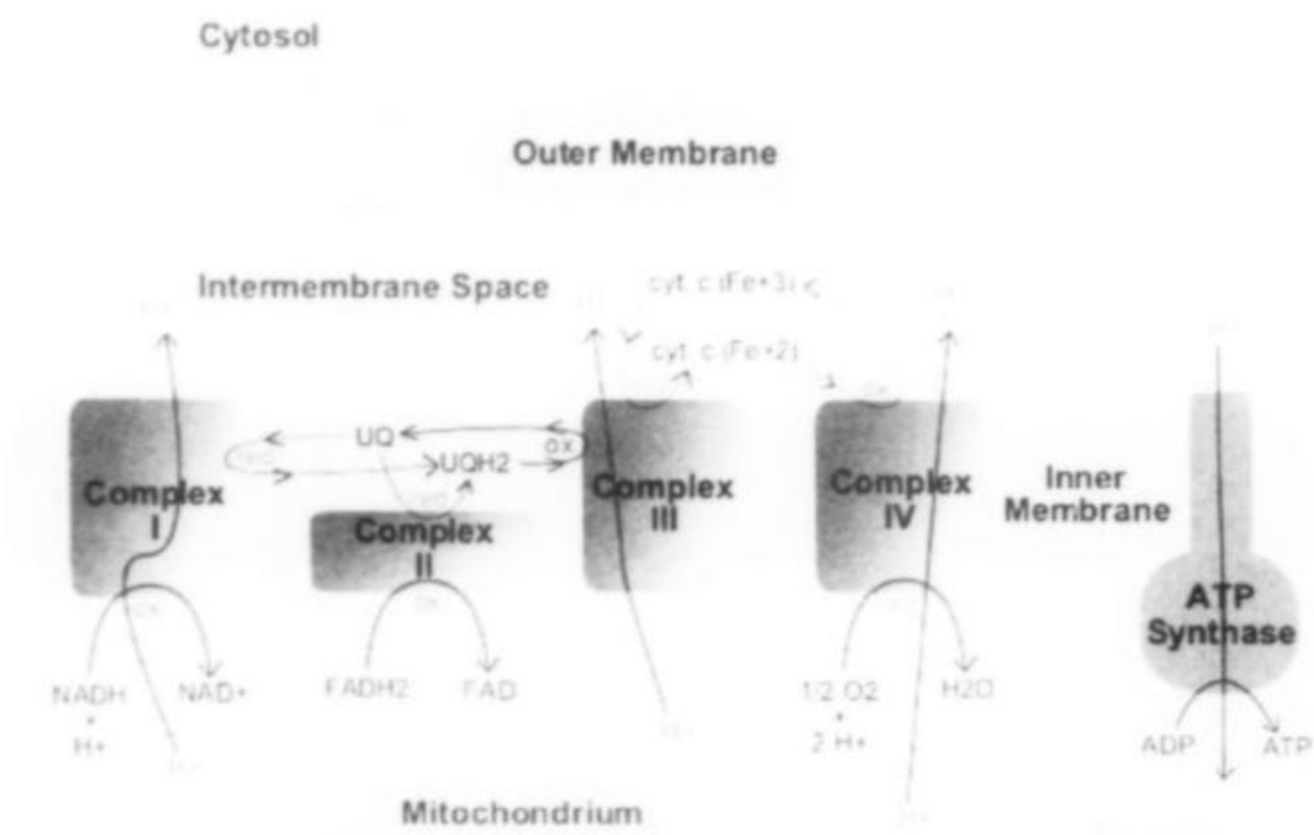

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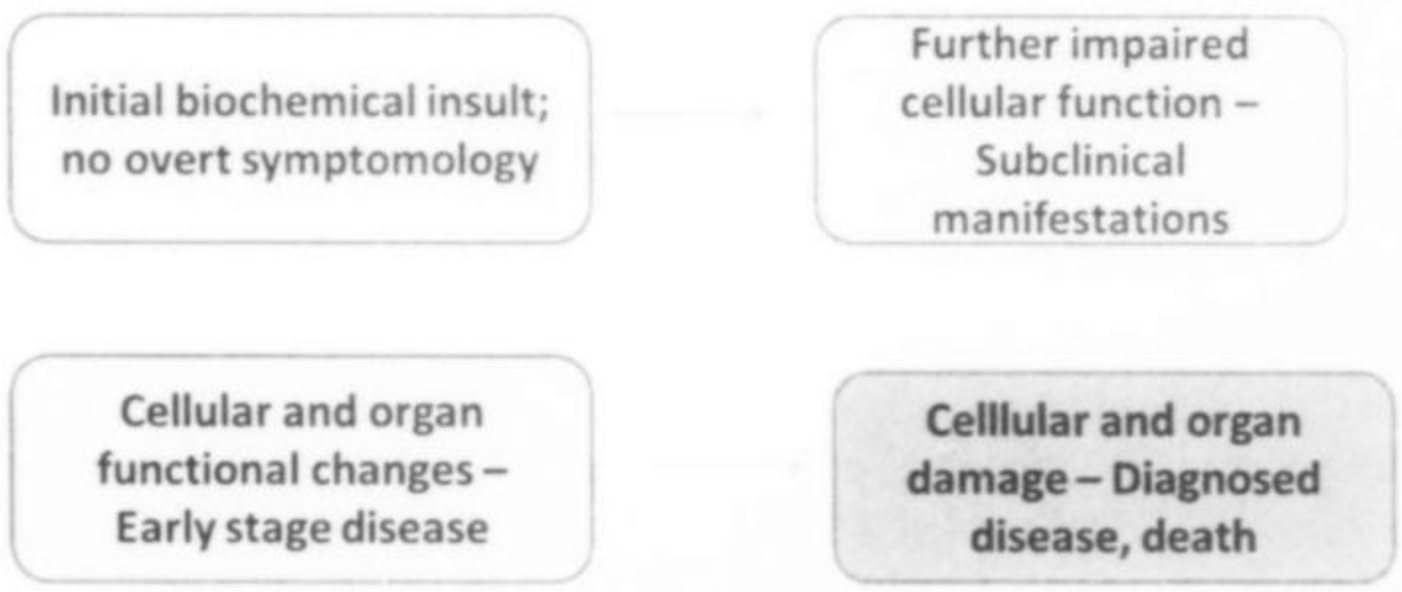

Apoptosis

Recall that another important role of mitochondria is that of regulating cellular apoptosis. Because ROS damage negatively impacts ATP production, necessary for ALL cellular functions, regulation of apoptosis is also affected. Apoptosis is the process of programmed cell death, necessary for the renewal of all body cells, and for the continuity of life. Approximately 30-50 billion cells are replaced daily in the average human. [15] However, too much apoptosis can cause muscle and organ failure, and too little may contribute to tumorigenesis.

Recall that the mitochondrial inner membrane is composed primarily of cardiolipin, an easily oxidized phospholipid. When the mitochondrial membrane is damaged (due to any of the stressors mentioned above), apoptotic signals are released which cleave to nDNA and initiate cell death. The more membrane damage, the more rapid cellular degradation occurs. Several proteins and other substances in the mitochondria initiate apoptosis. During this process, cytochrome C is released from the intermembrane space into the cytosol which causes cell death (after other substances are triggered and released). So although 30-50 billion cells are replaced daily, if apoptosis in one body system is greater than the number of cells replaced, systemic disease and/or organ failure ensues. As cells continue to die off through apoptosis, tissue function decreases, which eventually lead to symptoms and chronic degenerative disease (refer to boxes 2 and 3 in Figure 3).[13]

Chronic Disease, Cancer and Mitochondria

As discussed earlier, lacking histones and with lowered ATP production, mitochondria have limited ways of self-repair once damage from ROS has been inflicted. In this situation, cells cannot even make the RNA and DNA they require to function without mitochondria. When mtDNA becomes damaged, it is more difficult to copy accurately, resulting in errors of transcription, deletions and mutations. Oxidation from ROS results in a series of cellular insults: cell membranes lose their integrity, the proton gradient is diminished causing less ATP to be produced, cellular proteins necessary for all other cellular functions unfold and lose their affinity for their enzymes, and cytochrome C is released into the cytosol stimulating apoptosis, all in a continuous feed-forward cycle of cellular, tissue and organ dysfunction (chronic degenerative disease). Production of ATP is the key differentiator and chief purpose of mitochondria in the cell; they are the keystone to proper tissue and organ function and even gene regulation in humans. This point cannot be over-stated or over-emphasized; without fully functioning mitochondria, we cease to exist. Research is finding that cancer cells also exhibit increased mitochondrial damage by ROS.[9] As discussed above, ROS impedes the ETS, resulting in not only reduced production of ATP, but an excess of unoxidized NADH and pyruvate, which in turn get reduced to lactate. Additionally, high ROS concentrations permit histone acetylation to predominate, which accelerates (faulty) nuclear transcription and thus replication, and initiates the release of NFkB into the nucleus (a significant pro-inflammatory cytokine which also damages nDNA). At the same time, however, cell differentiation and apoptosis signals are silenced with histone acetylation, eventually resulting in over-replication favoring tumorigenesis. [16]

Gonzalez et al further explained the connection between dysfunction in the ETS and apoptosis: more CO is produced as a by-product of inefficient cellular respiration, which also blocks apoptosis. Cancer cells have a lower proton gradient: only -15 mV compared to a normal cell of 50-70 mV. A reduced gradient simultaneously reduces ATP output. Complicating this metabolic scenario is the fact that without sufficient ATP, cells lose their ability for cell-to-cell communication, so as "individualized" unicellular cells, must form colonies to survive, forming what we know as the tumor. Thus, cancer is a cell survival mechanism in a hostile (acidic) environment, since cancer cells have a hard time surviving in an alkaline environment.[16] ROS contributes both to chronic disease manifestation through the mechanisms of mitochondrial dysfunction and subsequent tissue/ or-

gan loss of function; as well as tumorigenesis progression through the mechanisms of uncontrolled nDNA replication without differentiation. Cancer cells appear to thrive under anaerobic conditions; this phenomenon was first observed by Warburg in the 1930s.

Early History of Cancer Research – Warburg, Szent-Gyorgyi, and Pauling

According to the CDC, cancer (all forms) is now the second-leading cause of mortality among people in the developed world, exceeded only by heart disease.[17] By its nature and characteristics, cancer is the uncontrolled overgrowth of cells which we call a tumor. Normal cellular functions initiated by the mitochondria such as apoptosis, and cellular division/ replication are dysfunctional in a cancerous environment, due to loss of cellular membrane integrity, and an increasing acidic cellular environment, as stated above. When cellular functions no longer operate properly, the cell accumulates ROS and lactate, leaving the cell to depend on anaerobic glycolysis for energy, which generates only two ATPs.[10]

Our experience has revealed that conventional oncology believes that a significant proportion of cancers are the result of genetics, yet recent statistics inform us that genetics play a role in only 5% of cases.[18] We now know that mitochondrial activity/ function determines whether oncogenes get "switched on" or "off;" an alkaline diet appears to help keep these genes under control.

Otto Warburg, a German biochemist, was a pioneer in observing and publishing research into cellular respiration and the effects on cancerous cells/ tumor growth; he was awarded the Nobel Prize in Physiology in 1931 for his work. His research concluded that, unlike normal cells which depend on aerobic oxidative phosphorylation to produce ATP, cancerous cells instead use anaerobic respiration for energy production. As he wrote and lectured, "The prime cause of cancer is the replacement of the respiration of oxygen in normal cells with the fermentation of sugar. All normal cells meet their energy needs by respiration of oxygen, whereas cancer cells meet their energy needs in great part by fermentation. Thus, cancer cells are partial anaerobes." He added, "During cancer development aerobic respiration fails, fermentation appears, and highly differentiated cells are transformed into fermenting anaerobes, which retain only the now useless property of growth." He concludes, "Cancer is ultimately a problem of how cells use or misuse oxygen to burn sugars."[19] Sadly, this theory was discounted by the mainstream medical establishment, continued to be discounted throughout the 1960s when Warburg lectured internationally, and continues to be ignored by today's oncologists who refute the role of anaerobic glycolysis, sugar and ROS in the creation of cancerous conditions. Research done by Vaughn and Deshmukh demonstrate that it is "glucose metabolism which protects cancer cells from cytochrome C mediated apoptosis."[20] Albert Szent-Gyorgyi, who won the Nobel Prize in Physiology in 1937 for his work in discovering vitamin C elucidated what was the theory of cellular combustion (producing energy), i.e., that "the combustion of hydrogen is the real energy-supplying reaction."[25] Empirical experimentation with Hungarian paprika and lemons had a therapeutic effect on colleagues with damaged capillary blood vessels; the positive effect of vitamin C on blood vessel integrity and wound-healing is well-documented. Vitamin C is also a powerful RedOx agent and co-factor in many enzymatic reactions.[21]

Following on the research of Warburg and Szent-Gyorgyi, in the 1970s Linus Pauling conducted empirical studies of both oral and IV vitamin C on people with cancer and the common cold, reasoning that vitamin C therapy increased survival of cancer patients by four times compared to control groups. He co-wrote a book entitled "Vitamin C and Cancer" and with a colleague Ewan Cameron, but was still labeled a "quack" by the medical establishment. Gonzalez et al wrote that ascorbate (vitamin C) may preferentially target the mitochondria by increasing electron flux, thus increasing the production of ATP and thus, the "normalization" of the apoptosis function. They added that a greater amount of vitamin C optimizes the production of ATP as well as cell-to-cell communication and cell

differentiation.[16] Further research remains important with regards to both the dosage of vitamin C as well as the timing of application during oncologic therapies, as Vitamin C can have both antioxidant and pro-oxidant characteristics.[22] RedOx therapy may become the "medicine of the 21st century.

A recurring theme is that mainstream allopathic oncologists continue to deny the efficacy of vitamins, minerals, whole foods and antioxidants on prevention and treatment of chronic degenerative diseases and cancer. With the overview of biochemical processes involved in mitochondrial and cellular dysfunction as outlined in this paper, the evidence appears to be strong that an alkaline diet high in antioxidants (fruits and vegetables) would help prevent chronic degenerative disease and cancer, and lead to a better quality of life.

The Protective, Preventive Action of an Alkaline Diet

Prevention of cancer involves two elements: consumption of the proper diet and the avoidance of substances that damage the mitochondria. Damage to mitochondria is known to have a key role in the pathogenesis of an extensive amount of disorders such as schizophrenia, dementia, Alzheimer's disease, epilepsy, strokes, neuropathic pain, Parkinson's disease, ataxia, transient ischemic attack, cardiomyopathy, coronary artery disease, chronic fatigue syndrome, fibromyalgia and diabetes among others. A proper diet must include sufficient nutrients to sustain efficient aerobic respiration. This includes the macronutrients that are the energy and macromolecules for functional and structure and function and the micronutrients that facilitate efficient functioning of the biochemical pathways to extract and transform energy into a biologically useful form. These micronutrients include the B-complex, various minerals, other cofactors such as CoQ_{10}, lipoic acid and acetyl L carnitine and the electrolyte balance to promote the conditions for an efficient physiological functioning.

Risk factors linked with chronic diseases (e.g., cancer, lung diseases), such as stress, tobacco, environmental pollutants, radiation, infection, cause damage to cells through excessive or uncontrolled generation of ROS.[23]

Xenobiotics that damage mitochondrial membrane include environmental toxicants and medications. Tobacco smoke reduces arterial oxygenation and increases oxidative stress and decreases cytochrome oxidase in complex IV if the mitochondria, 25% after 30 minutes of passive smoke and the enzyme activity continues to decrease with time.[24]

Because the mitochondria is crucial in energy production, the mitochondrial dysfunction can be related to various groups of diseases including the main killers in our society cancer and cardiovascular disease.[25] Other environmental factors include some insecticides and pesticides and fat soluble chemicals with benzene rings such as hair dye and paint fumes.

Research has demonstrated that medications are a major cause of mitochondrial damage, which may explain many adverse effects. These offenders include psychotropic drugs, anticonvulsants, anti-cholesterol medications, analgesics and anti-inflammatory agents, antibiotics, steroids, anticancer chemotherapy, Diabetes medications and HIV/AIDS medications. While certain nutritional cofactors might limit the damage caused to mitochondria by medications, there is still much research needed in this area.[26]

Chronic inflammation can stimulate all stages of tumorigenesis, (DNA damage, uncontrolled replication, inhibition of apoptosis, augmented angiogenesis and tissue invasion/metastasis. Chronic inflammation is prompted by environmental factors (e.g., infection, tobacco, asbestos) and host gene mutations factors (e.g., Ras, Myc, p53). Despite the extensive research published over the last decade, many of the precise molecular mechanisms are still in elucidation and discussion.

It has been proposed that activation of Ras, Myc, and p53 cause mitochondrial dysfunction, which then causes mitochondrial reactive oxygen species (ROS) production and consequent signaling transcription factors (eg, NFkappaB, STAT3, etc.) that promote inflammation-associated cancer.[27] However, the bioenergetic theory of carcinogenesis[28] proposes that mitochondrial dysfunction could

be the original insult that induces signaling that activates the oncogenes and transcription factors. Inflammation-associated cancers produced from signaling from the mitochondrial are being identified that may prove useful for developing innovative strategies for both cancer prevention and cancer treatment.

Diet and Biochemical Conditions

Neustadt suggests that because the major reason and root cause for mitochondrial dysfunction (and thus chronic disease and cancer) lies in a surplus of ROS that cannot effectively be neutralized, that RedOx therapy (IV vitamin C, alkaline diet, supplements, enzymes, etc) may be a viable lifestyle option for both prevention and treatment. Because research is still lacking in the dosage and timing of reductive therapy, the best way to determine vitamin and supplement needs is through urinary organic acid testing. Optimal mitochondrial function is dependent upon sufficient vitamins, minerals, enzymes, co-factors and all the nutrients necessary for optimal cellular function, all of which are found in a good alkaline diet.[1] Cancer cannot exist in an alkaline, oxygen-rich environment. To overcome cancer, we must change our internal environment.[9] This is the mitochondrial correction concept.

The co-factors necessary for complete Kreb's Cycle metabolism include cysteine, sulfur, iron, magnesium, manganese, lipoic acid, niacin, thiamin, riboflavin, and pantothenic acid, the last four of which are in the Vitamin B family. Supplementation with lipoic acid and acetyl-L-carnitine can improve mitochondrial function.[29] Carnitine is necessary to move Acetyl-CoA into the mitochondria with vitamin C as a co-factor. The ETS requires both CoQ_{10} and flavins which include riboflavin, iron-sulfur complexes, copper and heme molecules. Heme synthesis requires pyridoxine (B_6), riboflavin (B_2), iron, copper, and zinc. Glutathione is a major anti-oxidant which requires selenium as a co-factor for production. Deficiencies in any of these substances can cause increased ROS production and loss of cellular function. Antioxidant herbs and supplements include such substances as turmeric (curcumin), green tea, resveratrol, and garden herbs such as oregano. Anti-inflammatory substances include Omega-3 fish oil, flax oil, vitamin E, boswellia, and ginger.[1]

Alkaline vs Acidic Environment

Average adult humans eating Western diets have chronic, low-grade metabolic acidosis at a grade that can be estimated by the net rate of endogenous non-carbonic acid production (NEAP), which varies with diet. [30] Some age-related problems such as bone mass decline, osteoporosis, and decrease in muscle mass. Chronic, low-grade is in part caused by diet-dependent acidosis and may therefore be improved by diet modification and/or supplementation.

Our current "Standard American Diet" (SAD) is acidic, made so by over-consumption of high-glycemic foods, processed foods, sugar, meats, coffee and alcohol, and anything made with white flour. Stress and toxins also contribute to an acidic environment. Mitochondrial enzymes in the matrix work best in an alkaline environment, thus optimizing their metabolic processes.[31,32] According to Gonzalez, alkaline solutions absorb oxygen, whereas acidic environments expel oxygen, which explains why anaerobic organisms thrive in an acidic environment, and why tumorigenesis is also favored in an acidic environment. A lowered pH contributes to a lowered membrane potential which results in cellular dysfunction and lowered ATP production, again, favoring chronic disease progression and carcinogenesis.[16]

The ideal blood pH range is 7.35 to 7.45, with the majority of holistic health practitioners preferring the higher range, closer to 7.4. One of the chief ways the body creates homeostasis is to "steal" minerals from bones and other vital organs. This compensating mechanism, of course, contributes to loss of vital co-factors involved in important enzymatic reactions, which in turn decreases cellular and organ function eventually leading to chronic disease and/or cancer.

Concluding Remarks

Developing a healthy lifestyle, with an emphasis on increasing vegetables in the diet, would decrease ROS and provide the or-

ganism with a balance of nutrients that fosters a healthy biochemical environment that strengthens the composition and function of the mitochondria should be protective against chronic diseases such as cancer.

Competing Interests

The authors of this report declare that they have no competing interests.

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The Adjunctive Treatment of Epilepsy with Orthomolecular Substances

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Abstract *Epilepsy can be understood as a disorder of abnormal brain electrical activity resulting in recurrent seizures. Underlying the abnormal brain activity are defects in gamma-aminobutyric acid (GABA) activity, GABA receptor inhibition, and even defects in the intracellular buffering of calcium. The mechanisms underlying the increased excitation include increased activation of N-methyl-D-aspartate receptors (NMDARs) and other processes. This article describes specific orthomolecules that possess anti-seizure activity by either up-regulating the GABA system and/or down-regulating the NMDAR system. Several patient cases are highlighted to show the potential benefits from this approach. Some case management tips are provided to assist clinicians in understanding how to implement this approach with their patients. Given how safe and cost-effective the orthomolecular approach is, this article asserts that the use of specific orthomolecules should be considered when patients (after having made an informed decision) want to complement their anticonvulsant medication, seek an alternative to anticonvulsant medication, or have not responded adequately to their anticonvulsant medications.*

Introduction

Epilepsy can be understood as a disorder of abnormal brain electrical activity resulting in recurrent seizures. It is diagnosed as a neurological disorder when there has been two unprovoked seizures.[1] Seizures result in clinical signs or symptoms that depend on "the extent and pattern of the propagation of the epileptic discharge in the brain."[1] Some possible causes of seizures include genetic predisposition, trauma, cerebrovascular accident, brain tumours, alcohol and drug withdrawal, and other conditions.

Brief Overview of Pathophysiology

In the cerebral cortex a network of cortical neurons can manifest seizure activity when "a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons in favour of a sudden-onset net excitation."[1] When the visual cortex is affected, visual manifestations can result. Other clinical manifestations (auditory, taste, and motor symptoms) can arise when the affected cortical network gets disrupted in specific sensory, gustatory, or motor areas.

The genesis of seizures arises from complex biochemical processes of reduced inhibitory activity and increased excitatory activity.[1] Underlying the abnormal cortical activity and decreased inhibition are defects in gamma-aminobutyric acid (GABA) activity, GABA receptor inhibition, and even defects in the intracellular buffering of

calcium. The mechanisms underlying the increased excitation include increased activation of N-methyl-D-aspartate receptors (NMDARs) and other processes.

Diagnostic Considerations

Referral to a neurologist is necessary in the evaluation of a patient suspected of having epilepsy. Serum prolactin levels can be elevated 3- or 4-fold following a seizure, but this only has relevance in generalized tonic-clonic seizures compared to other types.[1] To firmly establish a diagnosis, the neurologist will need to do two neuroimaging studies (e.g., head computed tomography/CT scan and brain magnetic resonance imaging/MRI) to assess for structural abnormalities, and electroencephalography (EEG) to assess for interictal epileptiform discharges or focal abnormalities.[1]

Orthomolecular Therapeutics

The epileptic patients who have sought out treatment from me have tended not to respond adequately to their anticonvulsant medications or do not want to take medications at all. I have seen many such patients report fewer seizures and less intense seizure activity when orthomolecules* were added to their existing anticonvulsant medication. I have also treated a handful of patients who chose not to take anticonvulsant medication. One such paediatric patient has remained seizure-free for more than 13 months. An adult patient remained seizure-free for eight months and then I lost contact with him. Another patient remained seizure-free for almost five months before we decided that the more appropriate path was to pursue anticonvulsant medication. Thus, I have observed some intriguing responses from orthomolecular treatments, and as a result, I am convinced that a number of orthomolecules possess anti-seizure properties that can facilitate noteworthy quality of life enhancements.

* The term, Orthomolecule, refers to substances found naturally or normally in the human body, such as amino acids, essential fatty acids, hormones, minerals, and vitamins.

Vitamin B_6

It is important to distinguish whether vitamin B_6 is given to guard against a deficiency, or is given to treat non-vitamin B_6-dependent epilepsy. I will not address vitamin B_6-dependent epilepsy since these usually occur within months of birth and can be controlled rather well with large supplemental doses of vitamin B_6.[2] Deficiency of vitamin B_6 is usually associated with the use of phenytoin.[3]

Three studies have shown that patients with epilepsy being treated with phenytoin are vulnerable to vitamin B_6 deficiency.[3-5] Some studies have shown supplemental vitamin B_6 to help with non- vitamin B_6-dependent epilepsy. In one study, 26 patients were given 160 mg/day of vitamin B_6.[6] Of the 26 patients, 19 were identified as having vitamin B_6 deficiency per an abnormal tryptophan load test. Nine of the patients had a complete (no seizure activity) or partial response (less seizure activity) to the vitamin, and some of these patients were able to discontinue their anticonvulsant medication. In another study, vitamin B_6 (20 mg 3-6 times/day) was given to 14 patients between 2 and 17 years of age.[7] Five patients had a complete response while three patients had a partial response to the vitamin. All of the patients in this study suffered from petit mal seizures, and one of the patients also had grand mal epilepsy. There are other positive studies and even some negative ones where vitamin B_6 did not help and actually worsened the clinical outcome. For a thorough review of many of the studies on vitamin B_6, please see Gaby.[8]

Dosage: To prevent deficiency of the vitamin for patients on phenytoin, Gaby recommends a daily dose of 10-50 mg. When using larger doses, Gaby recommends caution since high-dose vitamin B_6 can interfere with some anticonvulsant medications. He advises clinicians to add supplemental magnesium since vitamin B_6 increases the requirement for magnesium. The therapeutic range for vitamin B_6 is 60-200 mg/day, although higher daily doses might sometimes be needed.

The active form of vitamin B_6 (pyridoxal

phosphate/PLP) is more potent than regular vitamin B_6 as pyridoxine hydrochloride. I recommend that PLP be tried initially. The therapeutic dose of PLP should be in the range of 7-38 mg/kg/day.[8] For both forms of vitamin B_6, especially at high doses, watch for signs of toxicity (albeit, rare) such as peripheral neuropathy, central nervous system toxicity, elevated liver enzymes, and nausea and vomiting.

GABA

This amino acid functions as an inhibitory neurotransmitter. There are two forms of GABA available: crystalline GABA and PharmaGABA® (produced by a fermentation process that utilizes *Lactobacillus hilgardii*).[9] Both forms have the same molecular structure and mechanism of action, and therefore it is unscientific to contend that one form somehow traverses the blood-brain barrier while another form does not.[10]

PharmaGABA® has been shown to favourably moderate various biochemical markers of stress.[9] In a study (n=13) that evaluated the therapeutic effects of PharmaGABA®, 60 minutes after ingesting 100 mg, the electroencephalographic readings showed statistically significant increases in alpha waves ($p<0.05$) and decreases in beta waves compared to results obtained when the same subjects were administered L-theanine and water.[11] Since these results showed PharmaGABA® to possess relaxation and anti-anxiety effects by increasing the production of alpha waves, this might be how it potentially moderates seizure activity.

Crystalline GABA has been given orally in certain cases of status epilepticus and has been effective.[12] One major study of crystalline GABA and vitamin B_6, as cited by Braverman et al, was purported to show improvement in 50% of the 699 epileptics given these supplements.[12] After having fully reviewed the original study[13] cited by Braverman et al, I have not been able to confirm that a human study involving 699 subjects actually took place. Thus, it is my opinion that Braverman et al either referenced the wrong study in their book, or they simply did not read the actual study they cited.

Dosage: I prefer the PharmaGABA® form based on my own empirical observations. The crystalline form usually comes in much higher doses per pill, such as 500 mg or 600 mg, and these doses now seem unnecessary. Crystalline GABA in doses of 1 to 3 grams per day might cause neurologic tingling and a flushing sensation.[12] I have found that 200-400 mg per day of PharmaGABA® produces anti-seizure effects when administered at bedtime, or even in the morning before breakfast. I have not observed any side effects from PharmaGABA®. The PharmaGABA® preparation has been tested in rats that were administered doses of 5,000 mg/kg.[9] There were no deaths and the LD50 was determined to be >5,000 mg/kg.

Taurine

The anti-seizure effects are probably the result of its membrane-stabilizing properties (it appears to normalize the flow of sodium, potassium, and calcium into and out of the cell).[14] Taurine might also help decrease seizure activity by lowering glutamic acid levels through the enhancement of glutamic acid decarboxylase.[14]

Dosage: According to Gaby, taurine has been administered orally and intravenously at doses ranging from 200 mg/day to 21 g/day.[8] The standard therapeutic dose is between 100 and 500 mg/day, even though 1.5 g/day was shown to induce anti-seizure activity in some patients in a published report.[8] The effective dose in rats is equivalent to 3.5-7 g/day in a 70 kg man, but doses in this range and even above 500 mg/day might cause amino acid imbalances and render this treatment ineffective.[8,15]

In a review article on the therapeutic applications of taurine, Birdsall noted that various trials have used between 375-8,000 mg/day providing outcomes with an efficacy somewhere between 16-90%.[16] Birdsall believes Taurine's dubious efficacy is the result of its "limited diffusibility across the blood-brain barrier," which may limit this amino acid from having strong anti-seizure effects.[16] My clinical experiences with taurine

have been positive. I have not observed any toxicity and have been unable to ascertain if it actually does lead to concerning amino acid imbalances when used for more than a couple of months.

Magnesium

Pfeiffer reported that a magnesium deficiency induces muscle tremors, depression, irritability, and occasionally convulsive seizures.[17] He cited the work of the late Adelle Davis who reported success in controlling seizure activity with 450 mg/day of magnesium, which apparently allowed patients to discontinue their anticonvulsant medications. Elevated N-methyl-D-aspartate and its metabolites can produce experimental seizures. Magnesium is a natural inhibitor of N-methyl-D-aspartate, and should be used to treat patients having both epilepsy and elevated levels of these compounds in their blood.[18] Some research has confirmed Pfeiffer's observations, in that magnesium depletion can both cause and increase seizure activity in response to seizure-inducing stimuli.[18,19] There is also data demonstrating lower levels of magnesium in both the serum and cerebrospinal fluid among patients with grand mal epilepsy compared to controls.[20,21]

Dosage: For optimal dosing of magnesium, patients should be given 5-30 mg/kg/day.

Case 1: Paediatric patient with MRI results suggestive of focal cortical dysplasia

This 7-year old patient presented to my private clinical practice (Toronto, Ontario) in November 2012. The first seizure occurred when she was six years old. The video EEG (June 2011) results during the awake and drowsy states demonstrated very active epileptiform spike slow wave discharges with an associated slow wave abnormality arising from the right posterior temporal region with infrequent spread into the left posterior temporal region. The subsequent MRI showed brain abnormalities suggestive of focal cortical dysplasia. At my initial evaluation, the patient's parents reported seven seizures in the preceding 16 months. They all happened at night. The patient also had a history of recurrent streptococcal pharyngitis, accompanied by chronically enlarged tonsils.

The parents wanted to try an orthomolecular approach since their daughter was unable to tolerate anticonvulsant medication due to an allergic reaction to carbamazepine and intolerant side effects from divalproex sodium. I prescribed the following: vitamin C (500 mg twice daily); omega-3 essential fatty acids (one teaspoon daily providing 320 mg of eicosapentaenoic acid, 200 mg of docosahexaenoic acid, and 50 mg of gamma-linolenic acid); vitamin B_6 (100 mg twice daily); magnesium-taurine (providing 200 mg of magnesium and 600 mg of taurine daily); and PharmaGABA® (200 mg at bedtime).

At the second visit (February 2013), the parents reported that the patient had a seizure in early December, but none since. They also had their daughter scheduled for tonsillectomy in March 2012. I increased the magnesium-taurine combination to three pills daily (providing 300 mg of magnesium and 900 mg of taurine).

At the third visit (August 2013), the parents reported that the surgery went well without incident. Their daughter had two seizures since the prior appointment (one in May and another in early August). I increased the PharmaGABA® to 400 mg at bedtime until the next follow-up.

At the forth visit (December 2013), the parents reported only one seizure since the last visit that happened in September. They noted results from the orthomolecular approach and were pleased with its absence of sedating effects.

At the most recent visit (November 2014), the parents reported that their daughter has been seizure-free since September 2013, approximately 13-14 months. They have seen their neurologist who was delighted with this news and told them to remain on the orthomolecular plan unless another seizure should occur.

The latest video EEG (June 2014) did not show any EEG seizures during the awake and sleep period. This patient is now 10 years old and enjoys her life, does well in

school, and barely thinks about the seizures that once consumed her life.

Her plan was modified to the following: magnesium-taurine (provides 130 mg of magnesium and 600 mg of taurine daily); vitamin B_6 (200 mg daily); PharmaGABA® (400 mg at bedtime); and the recommendation to continue with the same dosages of omega-3 essential fatty acids and vitamin C (as described previously).

Manganese

This trace mineral plays a significant role in cerebral metabolism and performs several physiological functions that include: (1) being a critical cofactor for glucose utilization within the neuron; (2) increasing adenylate cyclase activity (converts ATP --> cAMP); and (3) neurotransmitter control.[22] Like magnesium, there are studies demonstrating that patients with epilepsy have lower whole-blood manganese levels (20-41% lower) compared to controls.[23-28]

Dosage: The adult dose of manganese to control seizures is 15-30 mg/day, and it has a low level of toxicity.[22]

Zinc

Seizures might result when zinc-to-copper ratios fall in the absence of adequate taurine.[29] Deficiency of zinc or an elevated copper-to-zinc ratio (without adequate taurine) might therefore have a role to play in the genesis of seizures. Zinc might also reduce seizure activity by inhibiting aspartic acid neurotransmission.[15]

Dosage: The therapeutic dose of elemental zinc is probably in the range of 10-80 mg/day. Consideration should be given for simultaneous copper supplementation (i.e., 1-2 mg/day) if high doses of zinc (i.e., at or above 80 mg/day) are prescribed for more than a couple of years due to potential haematological problems resulting from chronic high-dose zinc supplementation.

Case 2: Dilantin resistance

This case was reported in the book, *Healing Nutrients Within*.[14] I include it here because the favourable effects were the result of combining taurine, manganese, and zinc.

"At the Brain Bio Center, we gave taurine successfully to many patients with seizure disorders. A sixty-six-year-old man with a history of seizures recently came to us. He had been put on Dilantin, but it failed to control his seizures. We maintained his dose of Dilantin but supplemented it with optimal doses of taurine (4 g), manganese (100 mg) and zinc (60 mg). Six months later, he was still free of seizures and his dose of Dilanitin was reduced."

Chromium (for consideration in suspected hypoglycaemia-associated seizures)

Gaby has suggested that both hypoglycaemia and hyperinsulinaemia might be involved in the pathogenesis of epilepsy.[8] Chromium has the most documented evidence to support its use as a blood-glucose-stabilizing molecule. For many years, chromium was thought to be involved in the glucose-tolerance factor (GTF) molecule that presumably increases insulin sensitivity. The composition of GTF, as isolated from yeast, is made of chromic ion, nicotinic acid, and the amino acids glycine, glutamic acid, and cysteine.[30] However, GTF of any type has never been found in human tissues. More recently, a naturally-occurring oligopeptide low-molecular weight chromium-binding substance (LMWCr) has been proposed to be the biologically-active form of chromium.[31] This compound has been found in many different types of mammals, and is widely distributed in numerous tissues (e.g., liver, kidney, spleen, intestine, testicles, and brain). This oligopeptide is also comprised of the amino acids glycine, cysteine, glutamic acid, aspartic acid, and has a multinuclear chromic assembly in which the chromic centers are bridged by the anionic ligands, oxide and/or hydroxide.[31] This LMWCr compound is part of an insulin amplification system that regulates glucose homeostasis through a complex series of biochemical reactions occurring at the insulin receptor.[32,33]

In one double-blind crossover experimental design study, eight female patients were given 200 mcg of supplemental chro-

mium (chromic chloride) for three months.[34] Supplementation improved the hypoglycaemic symptoms and raised the minimum serum glucose values 2-4 hours following the glucose load. Other improvements included an increase in the insulin receptor number and the binding of insulin to red blood cells. The authors of this study linked the aetiology of hypoglycaemia to impaired chromium nutrition and/or metabolism. In another study, 20 patients with clinical symptoms of hypoglycaemia were given 125 mcg of a yeast chromium supplement for three months.[35] Prior to taking chromium, 19 of 20 subjects had a minimal glucose level in the tolerance curve above 2.2 mmol/L (40 mg/dL), which is the limit for glucose-induced hypoglycaemia. The patients were assessed by the use of a glucose tolerance test (one gram of glucose/kg of body weight) and by an interrogation scheme. After three months of supplementation, 11 of 15 patients (73%) had improvements in the negative part of the glucose tolerance curve (i.e., the part of the curve being below the fasting level). Subjectively, the patients reported improvements in hypoglycaemic symptoms of chilliness, trembling, emotional instability, and disorientation. Thus, chromium as part of the LMWCr should have the ability to improve glucose tolerance, increase insulin sensitivity, and reduce suspected seizures if associated with episodes of hypoglycaemia.

In terms of toxicity, Lamson and Plaza have summarized the chromium literature, and evaluated its mechanisms of action and exceptional safety profile. According to these investigators, "there is no demonstration of general chromium toxicity in animals at a dose that would extrapolate to humans as 1,050 mg daily."[36] One of these investigators used 3,000-4,000 mcg of chromium as nicotinate given twice daily to adult-onset diabetic patients for months to years resulting in tremendous reductions of glucose and lipid levels without any increases in blood urea nitrogen, liver enzymes, or other laboratory abnormalities. It is interesting to note that high supplemental microgram doses of chromium would never come even close to 1,050 mg per day.

Dosage: I recommend 200-600 mcg/day of chromium for the treatment of suspected hypoglycaemia-associated seizures.

Case 3: Possible hypoglycaemia-associated seizures

I can recall a case of a patient in his twenties with a diagnosis of epilepsy who presented to the Robert Schad Naturopathic Clinic (Toronto, Ontario). He had two previous episodes of seizures. His neurologist was unable to determine the exact type and was considering complex partial seizures as the patient's diagnosis. During the seizures he experienced a partial loss of consciousness where he would lose sensations in his arms and feel paralysed, and some motor movements may have accompanied these episodes as well. He refused treatment with anticonvulsant medications and wanted to see if orthomolecular care would benefit his condition. His history revealed nighttime and early morning hunger, irritability when missing meals, and excessive cravings for sugar. We instituted dietary changes and gave him 400 mcg/day of supplemental chromium. We followed-up with this patient for approximately eight months after instituting treatment, and he no longer had any seizure episodes and felt well enough to resume his engineering studies.

Case 4: Generalized seizures possibly secondary to hypoglycaemia

This patient presented in 2008 with a probable diagnosis of generalized seizures when she came to my clinical practice (Toronto, Ontario). Her seizures were preceded by episodes of buzzing in the left ear followed by numbness ascending from the left foot to the left knee. Her initial EEG (April 2008) showed a potentially epileptiform disturbance over the right mid and posterior temporal region and to a lesser extent a similar independent finding over the left mid temporal region. Her MRI (May 2008) showed no space occupying lesion or focal abnormality of the temporal lobe. A subsequent sleep-deprived EEG was within nor-

mal limits and showed no epileptic activity.

At the first visit (November 2008), the patient informed me that she had five prior seizure episodes since they first began in March 2008. I diagnosed the patient with likely generalized seizures possibly secondary to hypoglycaemia. She was taking no anticonvulsant medication and also had her driver's license suspended as a result of the seizures. I prescribed the patient taurine (2,000 mg upon waking each day) and chromium (400 mcg at bedtime daily).

At the next appointment (December 2008) the patient reported one seizure since the initial appointment that was preceded by the typical buzzing sensations. I increased the taurine to 3,000 mg upon waking and the chromium to 600 mcg at bedtime. I also prescribed 1,500 mg of crystalline GABA to be taken at 10:30 pm each day.

At another follow-up (January 2009) the patient reported no seizures since the December appointment. No other treatments were prescribed.

In another follow-up (April 2009) appointment the patient reported no seizures since the December appointment even though she had four episodes of buzzing for the past four months without any evolution to seizure activity, however. I told her that she had to go for one full year of no seizure activity for her driver's licence to get reinstated. We were cautiously optimistic.

In May 2009, I received an email from the patient informing me that she had unfortunately experienced a seizure the Sunday evening. When she awoke, her bed was covered in urine and she had bitten her tongue. She was really upset since she went approximately five months with no seizure activity despite some buzzing.

We had our final visit (July 2009) and we agreed that she had to pursue anticonvulsant medication since the orthomolecular approach was unable to keep her seizure-free for 12 months. Since the patient reported possible seizure activity prior to her period, I instructed her to take 250 mg of vitamin B_6 and 150 mg of magnesium daily until our September or October follow-up. This was the last appointment I had with this patient. I assume she pursued anticonvulsant medication and exclusively worked with a neurologist.

Vitamin B_3

In Hoffer's review of the literature, both niacin and niacinamide were shown to have some sedative activity, and were able to potentiate the action of sedatives, anticonvulsant medications and certain tranquilizers. I recommend using niacinamide instead of niacin since this type of vitamin B_3 is seldom associated with cutaneous flushing. Niacinamide possess benzodiazepine-like effects,[38,39] which stimulate the GABA system and theoretically would reduce seizure activity. Benzodiazepines are used to manage seizures based on physiologic effects that are mediated through the GABA receptor.[40] It seems reasonable, therefore, to prescribe therapeutic doses of niacinamide to perhaps increase the anti-seizure efficacy of benzodiazepines and other anticonvulsant medications.

Dosage: The therapeutic dose needs to be adjusted according to each patient's clinical response. Start with 500 mg/day of niacinamide and slowly increase the dose until its efficacy can be determined. I would not increase the daily dose of niacinamide beyond 2,500 mg since larger doses can be associated with nausea and even vomiting.

Additional Orthomolecular Considerations

Gaby recommends that other nutritional supplements (e.g., vitamin E, biotin, folic acid, thiamine, and essential fatty acids) and specific diet modifications be considered as treatments for seizures.[8] He reviewed food allergy, the ketogenic diet, and even the Atkins diet as potential therapies. The reader is encouraged to review Gaby's article prior to instituting any of these additional treatments.

Clinical Management of Epilepsy

1. Let your patients know that the orthomolecular approach is probably not adequate to fully replace anticonvulsant medications.

2. The goals of instituting orthomolecu-

lar treatments are to increase overall quality of life, reduce the frequency of seizures, and to possibly reduce the amount of required medications. The orthomolecular approach is not meant to cure seizures.

3. Paediatric patients do not like taking pills of any kind, especially when they taste bad. When treating paediatric patients, work with the parents and think of creative ways to ensure compliance.

4. Hypoglycaemia is an overlooked possible cause of seizures. I believe that hypoglycaemia occurs more frequently in the adult cases. With the supplemental use of chromium and some dietary modifications, it should be possible to determine in a few months if the orthomolecular treatments are helping, and if hypoglycaemia was partly responsible for seizure activity.

5. Don't be discouraged if none of the orthomolecular treatments work. Some seizure cases can be very difficult to treat so educate your patients about realistic outcomes from the adjunctive use of orthomolecular medicine.

Conclusion

Epilepsy can be difficult to treat since some patients might be resistant to their anticonvulsant medications. At the very least, the orthomolecular approach probably provides some benefit in reducing the frequency and intensity of seizure activity. Given how safe and cost-effective the orthomolecular approach is, the use of the orthomolecules described above should be considered when patients (after having made an informed decision) want to complement their anticonvulsant medication, seek an alternative to anticonvulsant medication, or have not responded adequately to their anticonvulsant medications. More clinical studies are certainly needed, especially augmentation trials in which orthomolecules are taken alongside anticonvulsant medication. Until such trials happen, clinicians should feel comfortable recommending these specific orthomolecules to their patients based on evidence of anti-seizure activity.

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Competing Interests

The author declares that he has no competing interests.

Statement of Informed Consent

Written consent was obtained for cases one and four. Case Two was published in a book and the reference has been provided. Case Three was lost to follow-up and it has been impossible to find this patient.

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Personal Experience with Prostate Cancer

Introduction

From a routine medical check-up in February 2009 I discovered my PSA was 9.8. PSA or Prostate Specific Antigen is a substance in the blood which generally increases when there is a cancerous tumour in the prostate gland. Apparently there is little to worry about when the PSA is below 2.5 and everything to worry about if it reaches 20. A biopsy in April 2009 confirmed that I had prostate cancer. My family doctor told me it would undoubtedly need serious treatment because the tumour would grow, but the problem was not yet urgent. He advised me to have the treatment within a year.

Being a researcher all my professional life I recorded the progress of my condition diligently. Over the next ten months I spent more than 300 hours on the internet collecting information about my condition. I discovered a great deal which helped me understand important aspects of my condition. In this account, references on the more specific topics are cited, but it was not thought necessary to provide those on the more general statements.

From what I learned, radiation looked like the best option. I also consulted ten oncologists and urologists in several towns around Brazil. Maybe it was not surprising that the surgeons said surgery was the only solution and radiologists said it must be radiation.

I believe my problem has been totally resolved; my PSA has been low for more than five years since my trouble. Therefore, I decided to write of my experience in the hope that it might help others who are facing the same kind of trouble.

Cancer as I understand it

To be able to tackle the problem effectively I felt it important to understand the basics of cancer. The cells in our body are dividing all the time. This is what we know as growth and the natural replacement and repair of tissues. In all of us during our entire lives some cells divide wrongly. This is normal. In a healthy person the immune system identifies these faulty cells and eliminates them. Problems arise when they are not removed. If they are left unchecked they can grow into a cancerous tumour. This failure can come about in several ways.

1. If the body's immune system does not function efficiently it might not initiate the removal of the faulty cells. The immune system can be damaged when a person suffers stress over a long period.

2. In some situations the body might produce an excessive amount of almost all cells and this will necessarily increase the number of faulty ones. This can be a result of consuming dairy products and egg yolks. Both contain substantial amounts of natural growth hormones. These are substances that stimulate cell division. Stimulating cell division in a young animal is beneficial, but not in an adult. Milk is the natural food of young mammals that are growing. Humans are the only adult animals that consume large amounts of milk.

3. The body might produce an excessive proportion of faulty cells. This can be a result of intense radiation or exposure to carcinogenic chemicals like the heterocyclic aromatic amines found in charred and burnt food.

In many and perhaps in all cancers, two or all three of these factors work together to allow the tumour to develop.

My Condition

I have not smoked for more than forty years and have never consumed any other seriously carcinogenic substances so I very much doubt that they are an issue. My biggest problem was stress so the first question was how to minimize it. From the information I gathered from the Internet obviously there had also to be major changes in my diet. On the day I discovered that my PSA was high there were four types of cheese, two of yoghurt and two of ice cream in my fridge.

Stress

Eliminating most of the stress from one's life is surprisingly easy when one has to confront the alternative. Continued stress dam-

ages one's health so badly that it can have terrible effects. Friends and relatives understood and often helped out. Other people don't matter so much. I now try to avoid stressful people and situations. At times it was not easy and sometimes it cost me money. For example, if it was inconvenient to pay a bill on time then I paid it late and had to pay an excess charge; but so what?

Having a blood pressure gauge at home helps one control the stress. When one is stressed the blood pressure rises and this can happen without one feeling it.

Diet

I talked to ten oncologists and urologists about my condition. I asked all of them about the influence of diet on cancer. All insisted that diet is important for prevention, but is unimportant once a tumour has formed. I am told this is the generally accepted medical opinion, though not all hold to that view.[1] None was swayed by the argument that in the majority of cases their position is illogical. They are limiting their thinking to the formation of a first tumour and ignoring metastasis. From what I have read, prostate cancer kills no-one directly; it is the metastasis which is deadly. With any cancer, a diet that will reduce the chance of it spreading must be a wise strategy. Having said that, I accept that diet is unlikely to have any effect on the condition of someone who doesn't stop smoking cigarettes.

Once I had discovered I had a tumour I made radical changes to my diet. I cut out red meat, dairy products, processed food, drinks in plastic containers and alcohol entirely. I avoided glucose, bread and biscuits as much as possible. My diet was almost entirely fish, chicken, fresh vegetables and fresh fruits. Every day I took 4 or 5 grams of vitamin C, multi-vitamins, multi-minerals, B complex vitamins, Omega 3 and selenium. I drank green and black tea, soursop leaf tea, fresh fruit juices and lots of water. I did everything I thought might help. After all, this wasn't a scientific experiment with controls (of which I've conducted many). This was literally a matter of life or death.

After eleven months on this diet (February 2009 to January 2010) my PSA had dropped from 9.8 to 8.5. Obviously it would take some years at that rate for the PSA to drop to an acceptable level, but it was very encouraging that it was moving in the right direction and the tumour had not metastasized. To be frank, after 15 months on the diet it was difficult to face fish and chicken, and I was delighted to eat beef and pork and a bit of salami and gorgonzola again.

Here is a summary of the radical diet I followed (with a few comments).

Good Foods and Drinks

-Free range chicken, fish, shrimps and whole wheat flour are said to be acceptable.

-Polyphenols and other substances in plants are said to help reduce cancerous tumours.[2] Many foods and drinks are recommended. They are black and green tea, apples, avocados, several red fruits like water melon, tomatoes, guavas and grapes. Vegetables include beetroot, carrots, aubergine, sweet pepper, hot pepper, tamarind, beans, peas, lentils, nuts, salad leaves, cabbage, celery, broccoli, onions, garlic and ginger. Dark chocolate and vegetable oils (especially olive oil) are also advised.

-Black grapes and especially their seeds contain resveratrol which is known to be anti-carcinogenic.[3] I ate the fruits and cracked and chewed the seeds.

-Red wine also contains resveratrol but, to avoid the alcohol I drank pasteurized grape juice.

-Tomatoes and guavas contain lycopene (another anti-carcinogen). Water-melon contains higher concentrations of it.[4,5]

-Be careful about some of the advice. Beer is said to be good as it contains an anti-carcinogen, xanthohumol.[6] Apparently the problem is that you need to drink 17 glasses a day to obtain the necessary quantity of the desired substance.

Bad Foods and Drinks

-It is best to avoid beef, pork, animal fats, processed meats, smoked foods, white wheat flour, drinks in plastic bottles, glucose, and

alcohol in excess.

-Keep clear of all dairy products (milk, cheese, yoghurt, ice-cream, butter) and egg yolks. Biscuits and cakes contain eggs and milk or butter.

Dairy Products

None of the medics I consulted accepted the suggestion that dairy products could be involved in developing cancer. This story is very interesting. In Western Europe the incidence of breast cancer is 4%, whereas in China it is 1 in 10,000.[7] These facts have been known for two or three decades so an adequate explanation should have been found by now.[8] After all, the difference is 400 fold and the samples (totalling more than half a billion people) must be large enough to satisfy any critic. In general the Chinese don't consume dairy products. Dr Judith Plant (op. cit.) drew attention to the situation in 1987. Since then some research has been done on the question but not nearly enough.

The present attitude to the involvement of dairy products reminds me of linking smoking to lung cancer some years ago. There is a lot of circumstantial evidence, but little hard data. In fact the effects of natural growth hormones are far better documented than were those of nicotine during the early decades of that debate.[9]

Vitamin C

A similar situation obtains over the role of vitamin C as a cancer control.[10] Most in the medical profession do not accept it as a cancer treatment. It is enlightening to read some of the articles listed on the subject.[11]

The Treatment

In January 2010, I started six weeks of Intensity-modulated radiation therapy in Brasília. In this treatment an image of the tumour is placed on a computer programme and the computer controls the direction of the radiation guns. That way the aim of the guns is more accurate than when done manually and the collateral damage is greatly reduced.[12] This is especially important with prostate cancer as the prostate gland is squeezed between the bladder and the colon. Inaccuracy often has very unpleasant consequences.

During the first fortnight of treatment I felt nothing unusual and continued working normally. The second fortnight was rather tiring, but nothing untoward. The third fortnight was a nightmare. I was very weak and in considerable pain most of the time. Of course this was to be expected as the effect of the radiation is cumulative. For a couple of months after returning home I was still weak and I tired quickly and very easily.

My Present Health

The results of the radiation therapy were well worth the discomfort I suffered from the treatment. It was a great success and three months afterward my PSA was 0.25. Fortunately I have suffered no side effects and my life is more or less back to normal. Nowadays, I do my best to avoid stress and am careful with dairy products and processed foods. I have my PSA checked regularly. Since July 2010 it has been low; it is now 0.38.

Conclusions

Research the internet to be well informed.

-Find special items for your diet.

-Discuss your options, etc. with friends and relatives. They are sure to help; they'll be worried sick about you.

-When you consult your medic you need to know enough to ask the right questions and to understand the answers, and to know when you're being fobbed off.

-Identify the possible cause of your condition (smoking, stress, diet) and make the necessary changes to your life. Some people find it difficult to make the changes. If you love the people around you, you don't have any choice.

-It is very difficult, but try not to worry. Worrying results in stress and that will worsen the problem.

-Your determination to fight the problem is a vital factor. Think positively.

Final comment

Prostate cancer is an illness of older men. Therefore, on reaching 40 years of age it is important that you have your PSA checked regularly. If a cancer grows to the stage that you notice, it might well be too late.

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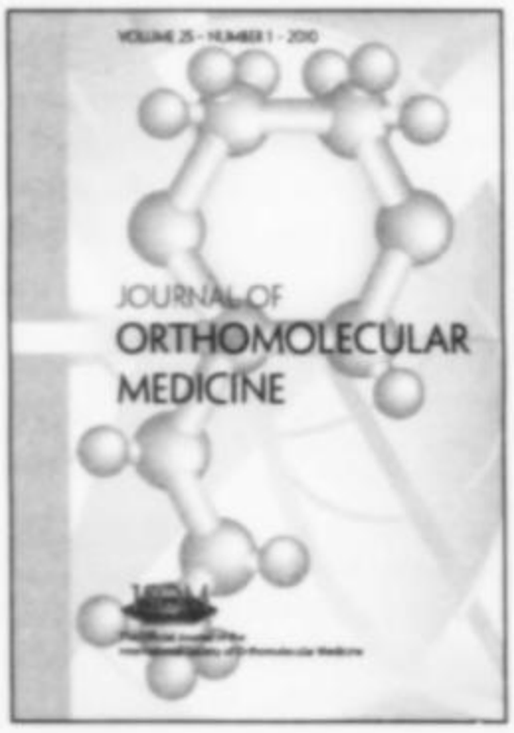

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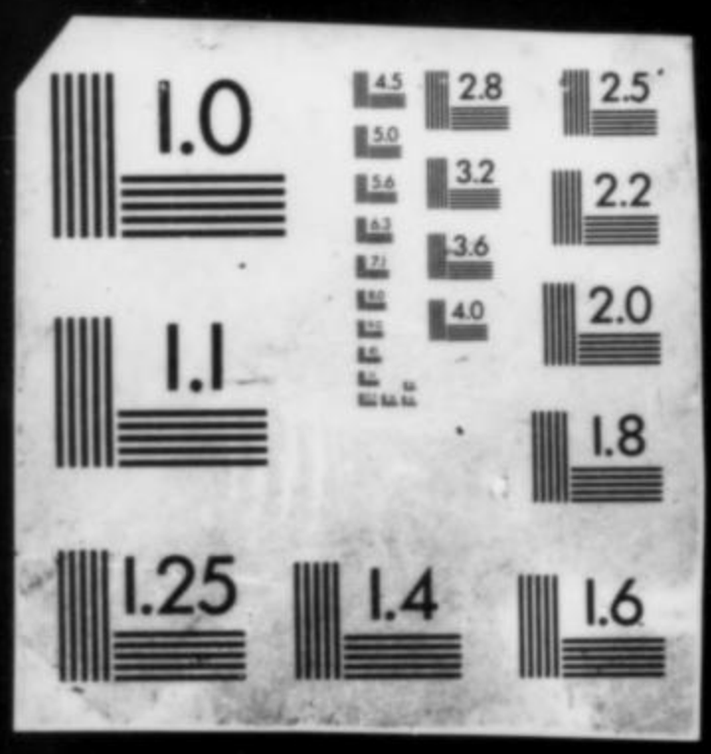
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